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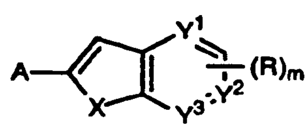
(54) Title: FUROPYRIDINE, THIENOPYRIDINE, PYRROLOPYRIDINE AND RELATED PYRIMIDINE, PYRIDAZINE AND TRIAZINE COMPOUNDS USEFUL IN CONTROLLING CHEMICAL SYNAPTIC TRANSMISSION



(I)

(57) Abstract

Novel heterocyclic ether compounds having the formula (I) wherein A, m, R, X, Y^1, Y^2 and Y^3 are specifically defined, which are useful in selectively controlling chemical synaptic transmission; therapeutically-effective pharmaceutical compositions thereof; and use of said compositions to selectively control synaptic transmission in mammals.

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Furopyridine, Thienopyridine, Pyrrolopyridine and Related Pyrimidine, Pyridazine and Triazine Compounds Useful in Controlling Chemical Synaptic Transmission

This application claims priority to United States Serial Number 60/001,619 filed July 28, 1995.

TECHNICAL FIELD

This invention relates to furopyridine, thienopyridine, pyrrolopyridine and related pyrimidine, pyridazine and triazine compounds which control chemical synaptic transmission; to therapeutically effective pharmaceutical compositions of these compounds; and to the use of said compositions to selectively control synaptic transmission.

BACKGROUND OF THE INVENTION

Compounds that selectively control chemical synaptic transmission offer therapeutic utility in treating disorders that are associated with dysfunctions in synaptic transmission. This utility may arise from controlling either pre-synaptic or post-synaptic chemical transmission. The control of synaptic chemical transmission is, in turn, a direct result of a modulation of the excitability of the synaptic membrane. Presynaptic control of membrane excitability results from the direct effect an active compound has upon the organelles and enzymes present in the nerve terminal for synthesizing, storing, and releasing the neurotransmitter, as well as the process for active re-uptake. Postsynaptic control of membrane excitability results from the influence an active compound has upon the cytoplasmic organelles that respond to neurotransmitter action.

An explanation of the processes involved in chemical synaptic transmission will help to illustrate more fully the potential applications of the invention. (For a fuller explanation of chemical synaptic transmission refer to Hoffman *et al.*, "Neurotransmission: The autonomic and somatic motor nervous systems." In: Goodman and Gilman's, The Pharmacological Basis of Therapeutics, 9th ed., J.G. Hardman, L.E. Limbird, P.B. Molinoff, R.W. Ruddon, and A. Goodman Gilman, eds., Pergamon Press, New York, **1996**, pp. 105-139).

Typically, chemical synaptic transmission begins with a stimulus that depolarizes the transmembrane potential of the synaptic junction above the threshold that elicits an all-or-none action potential in a nerve axon. The action potential propagates to the nerve terminal where *ion fluxes* activate a mobilization process leading to neurotransmitter secretion and "transmission" to the postsynaptic cell. Those cells which receive communication from the central and peripheral nervous systems in the form of neurotransmitters are referred to as "excitable cells." Excitable cells are cells such as nerves, smooth muscle cells, cardiac cells and glands. The effect of a neurotransmitter upon an excitable cell may be to cause either an excitatory or an inhibitory postsynaptic potential

(EPSP or IPSP, respectively) depending upon the nature of the postsynaptic receptor for the particular neurotransmitter and the extent to which other neurotransmitters are present. Whether a particular neurotransmitter causes excitation or inhibition depends principally on the ionic channels that are opened in the postsynaptic membrane (i.e., in the excitable cell).

EPSPs typically result from a local depolarization of the membrane due to a generalized increased permeability to cations (notably Na^+ and K^+), whereas IPSPs are the result of stabilization or hyperpolarization of the membrane excitability due to a increase in permeability to primarily smaller ions (including K^+ and Cl^-). For example, the neurotransmitter acetylcholine excites at skeletal muscle junctions by opening permeability channels for Na^+ and K^+. At other synapses, such as cardiac cells, acetylcholine can be inhibitory , primarily resulting from an increase in K^+ conductance.

The biological effects of the compounds of the present invention result from modulation of a particular subtype of acetylcholine receptor. It is, therefore, important to understand the differences between two receptor subtypes. The two distinct subfamilies of acetylcholine receptors are defined as nicotinic acetylcholine receptors and muscarinic acetylcholine receptors. (See Goodman and Gilman's, The Pharmacological Basis of Therapeutics, *op. cit.*).

The responses of these receptor subtypes are mediated by two entirely different classes of second messenger systems. When the nicotinic acetylcholine receptor is activated, the response is an increased flux of specific extracellular ions (e.g. Na^+, K^+ and Ca^{++}) through the neuronal membrane. In contrast, muscarinic acetylcholine receptor activation leads to changes in intracellular systems that contain complex molecules such as G-proteins and inositol phosphates. Thus, the biological consequences of nicotinic acetylcholine receptor activation are distinct from those of muscarinic receptor activation. In an analogous manner, inhibition of nicotinic acetylcholine receptors results in still other biological effects, which are distinct and different from those arising from muscarinic receptor inhibition.

As indicated above, the two principal sites to which drug compounds that affect chemical synaptic transmission may be directed are the presynaptic nerve terminal and the postsynaptic membrane. Actions of drugs directed to the presynaptic site may be mediated through presynaptic receptors that respond to the neurotransmitter which the same secreting structure has released (i.e., through an autoreceptor), or through a presynaptic receptor that responds to another neurotransmitter (i.e., through a heteroreceptor). Actions of drugs directed to the postsynaptic membrane mimic the action of the endogenous neurotransmitter or inhibit the interaction of the endogenous neurotransmitter with a postsynaptic receptor.

Classic examples of drugs that modulate postsynaptic membrane excitability are the neuromuscular blocking agents which interact with nicotinic acetylcholine-gated channel

receptors on skeletal muscle, for example, competitive (stabilizing) agents, such as curare, or depolarizing agents, such as succinylcholine.

In the central nervous system, postsynaptic cells can have many neurotransmitters impinging upon them. This makes it difficult to know the precise net balance of chemical synaptic transmission required to control a given cell. Nonetheless, by designing compounds that selectively affect only one pre- or postsynaptic receptor, it is possible to modulate the net balance of all the other inputs. Obviously, the more that is understood about chemical synaptic transmission in CNS disorders, the easier it would be to design drugs to treat such disorders.

Knowing how specific neurotransmitters act in the CNS allows one to speculate about the disorders that may be treatable with certain CNS-active drugs. For example, dopamine is widely recognized as an important neurotransmitter in the central nervous systems in humans and animals. Many aspects of the pharmacology of dopamine have been reviewed by Roth and Elsworth, "Biochemical Pharmacology of Midbrain Dopamine Neurons", In: <u>Psychopharmacology: The Fourth Generation of Progress</u>, F.E. Bloom and D.J. Kupfer, Eds., Raven Press, NY, **1995**, pp 227-243). Patients with Parkinson's disease have a primary loss of dopamine containing neurons of the nigrostriatal pathway, which results in profound loss of motor control. Therapeutic strategies to replace the dopamine deficiency with dopamine mimetics, as well as administering pharmacologic agents that modify dopamine release and other neurotransmitters have been found to have therapeutic benefit ("Parkinson's Disease", In: <u>Psychopharmacology: The Fourth Generation of Progress</u>, *op. cit*, pp 1479-1484).

New and selective neurotransmitter controlling agents are still being sought, in the hope that one or more will be useful in important, but as yet poorly controlled, disease states or behavior models. For example, dementia, such as is seen with Alzheimer's disease or Parkinsonism, remains largely untreatable. Symptoms of chronic alcoholism and nicotine withdrawal involve aspects of the central nervous system, as does the behavioral disorder Attention-Deficit Disorder (ADD). Specific agents for treatment of these and related disorders are few in number or non-existent.

A more complete discussion of the possible utility as CNS-active agents of compounds with activity as cholinergic ligands selective for neuronal nicotinic receptors, (*i.e.*, for controlling chemical synaptic transmission) may be found in U.S. Patent 5,472,958, to Gunn *et al.*, issued Dec. 5, 1995, which is incorporated herein by reference.

Existing acetylcholine agonists are therapeutically sub-optimal in treating the conditions discussed above. For example, such compounds have unfavorable pharmacokinetics (e.g., arecoline and nicotine), poor potency and lack of selectivity (e.g., nicotine), poor CNS penetration (e.g., carbachol) or poor oral bioavailability (e.g., nicotine). In addition, other agents have many unwanted central agonist actions, including

hypothermia, hypolocomotion and tremor and peripheral side effects, including miosis, lachrymation, defecation and tachycardia (Benowitz *et al.*, in: Nicotine Psychopharmacology, S. Wonnacott, M.A.H. Russell, & I.P. Stolerman, eds., Oxford University Press, Oxford, **1990**, pp. 112-157; and M. Davidson, *et al.*, in Current Research in Alzheimer Therapy, E. Giacobini and R. Becker, ed.; Taylor & Francis: New York, **1988**; pp 333-336).

Additional conditions for which neurotransmitter controlling agents may be useful include acute and chronic pain. (A. Dray and L. Urban, Annu. Rev. Pharmacology Toxicol. 36: 253-280, (1996).

A 6-bromo-2-(1-piperidinyl)thieno[2,3-b]pyridine of indeterminate use was disclosed by Meth-Cohn *et al.*, *J. Chem. Soc., Perkin Trans.*, 1:2509-17 (1981). Ciba-Geigy and Schenker et al. have disclosed various (2-benzofuranyl)-substituted tetrahydro pyridines and pyridines useful in treating mental depression (GB Patent No. 1,510,977, published May 17, 1978; and U.S. Patents No. 4,210,655 and 4,600,719). Toyama has disclosed N-BOC-thienopyridine derivatives having use an intermediates for preparation of complex cephalosporin-related antibiotic agents (PCT Patent Application WO 92/18505, published Oct. 29, 1992). Kabi Pharmacia has disclosed bicyclic heteroaryl compounds attached to a quinuclidene moiety useful for treating diseases related to muscarinic receptor function (PCT Patent Application WO 93/23395, published Nov. 25, 1993). Festal *et al.* have disclosed urea derivatives containing an azaindole moiety having utility as hypolipidemic and antiatheromatous agents (U.S.Patent No. 5,338, 849). Baker *et al.* have disclosed a class of substituted azetidine, pyrrolidine and piperidine derivatives having selective activity as agonists of 5-HT_1-like receptors (PCT Patent Application WO 96/04274, published Feb. 15, 1996).

SUMMARY OF THE INVENTION

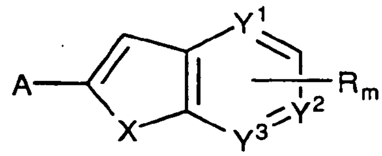
It has been found, in accordance with the present invention, that certain furopyridine, thienopyridine, pyrrolopyridine and related pyrimidine, pyridazine and triazine compounds are selective and potent cholinergic compounds useful in selectively controlling synaptic transmission.

In its principal aspect, the present invention provides a compound of formula (I) below, or a pharmaceutically acceptable salt thereof, wherein a monocyclic or bicyclic amine group is directly linked to a substituted or unsubstituted furopyridine, thienopyridine, pyrrolopyridine or related pyrimidine, pyridazine or triazine group.

Another aspect of the present invention provides pharmaceutical compositions comprising a therapeutically effective amount of a compound of formula (I) in combination with a pharmaceutically acceptable carrier or diluent.

In yet another aspect, the present invention provides a method for selectively controlling synaptic transmission in a mammal.

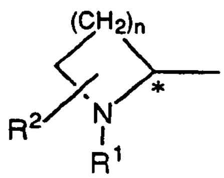
The novel compounds of the present invention are represented by formula (I):



(I)

or a pharmaceutically acceptable salt or pro-drug thereof wherein the group designated **A** is selected from the group consisting of:

(a)



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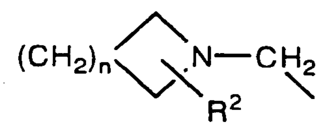
(b)



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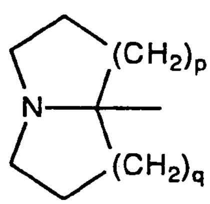
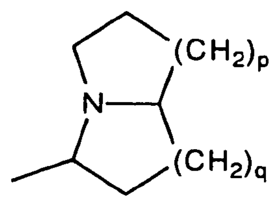
(c)



(d)



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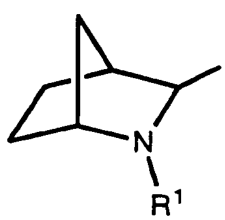
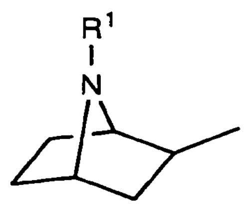
(e)



, and (f)



In the structures (a) through (f) shown above as alternative choices for the group A, the asterisk denotes a chiral center; m is 0, 1 or 2; n is 1, 2 or 3, and p and q are independently 1 or 2. The group R^1 is selected from the group consisting of H and C_1-C_3-alkyl; and R^2 is H, or when n is 2 or 3 is selected from the group consisting of C_1-C_3-alkyl, C_1-C_3-alkoxyl, hydroxymethyl, fluoromethyl, methoxymethyl, Br, Cl, F, OH, CN, -O-CO-CH_3 and -O-methanesulfonyl.

In the generic chemical structure shown above, **R** is independently selected at each occurrence from the group consisting of C_1-C_4-alkyl, bromo, chloro, fluoro, trifluoro-C_1-C_4-alkyl, trichloro-C_1-C_4-alkyl, COOH, CO_2-C_1-C_4-alkyl, CN, nitro, amino, NH-CO-C_1-C_3-alkyl, and NR^3R^3, wherein R^3 is H or C_1-C_3-alkyl.

The group designated **X** is selected from the group consisting of -O-, -S- or -NR^3, wherein R^3 is H or C_1-C_3-alkyl.

$\mathbf{Y^1}$, $\mathbf{Y^2}$ and $\mathbf{Y^3}$ are N or CH, with the provisos that at least one of Y^1, Y^2 and Y^3 must be N and when group **A** is selected from option (b), then Y^2 and Y^3 must be CH.

DETAILED DESCRIPTION OF THE INVENTION

Certain compounds of this invention may possess one or more asymmetric centers and may exist in optically active forms. Additional asymmetric centers may be present in a substituent group, such as an alkyl group. Compounds of the invention which have one or more asymmetric carbon atoms may exist as the optically pure enantiomers, pure diastereomers, mixtures of enantiomers, mixtures of diastereomers, racemic mixtures of enantiomers, diastereomeric racemates or mixtures of diastereomeric racemates. It is to be understood that the present invention anticipates and includes within its scope all such isomers and mixtures thereof. The terms "R" and "S" used herein are configurations as defined in <u>IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry</u>, *Pure Appl. Chem.*, **1976**, *45*: 13-30.

"C_1-C_3-alkyl" and "C_1-C_4-alkyl" refer to branched or straight-chain, unsubstituted alkyl groups comprising one-to-three or one-to-four carbon atoms, including, but not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, t-butyl and the like.

"C_1-C_3-alkoxyl" refers to a C_1-C_3-alkyl group, as defined above, containing an oxygen linker atom.

"Trichloro-C_1-C_4-alkyl refers to a C_1-C_4-alkyl group, as defined above, substituted with three chlorine atoms, including for example, trichloromethyl, 2,2,2-trichloroethyl, 3,3,3-trichloropropyl and 4,4,4-trichlorobutyl.

"Trifluoro-C_1-C_4-alkyl refers to a C_1-C_4-alkyl group, as defined above, substituted with three fluorine atoms, including for example, trifluoromethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl and 4,4,4-trifluorobutyl.

The term, "prodrug", refers to compounds that are rapidly transformed *in vivo* to yield the parent compounds of Formula (I), as for example, by hydrolysis in blood. T. Higuchi and V. Stella provide a thorough discussion of the prodrug concept in <u>Prodrugs as Novel Delivery Systems</u>, Vol. 14 of the A.C.S. Symposium Series, American Chemical Society (1975). Examples of esters useful as prodrugs for compounds containing carboxyl groups may be found on pages 14-21 of <u>Bioreversible Carriers in Drug Design: Theory and Application</u>, edited by E.B. Roche, Pergamon Press (1987).

The term, "prodrug ester group", refers to any of several ester-forming groups that are hydrolyzed under physiological conditions. Examples of prodrug ester groups include pivoyloxymethyl, acetoxymethyl, phthalidyl, indanyl and methoxymethyl, as well as other such groups known in the art.

The term, "administration", of the cholinergic agent or composition, as used herein, refers to systemic use as when taken orally, parenterally, by inhalation spray, by nasal, rectal or buccal routes, or topically as ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or transdermal patches in dosage form unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants and vehicles as desired.

The term "parenteral", as used herein, includes intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection as well as via infusion techniques.

By "pharmaceutically acceptable", it is meant those salts, amides and esters which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio, effective for their intended use in the treatment of psychological, neurological, cardiovascular and addictive behavior disorders. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, *et al.* describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, **66**: 1-19, **1977**. The salts may be prepared *in situ* during the final isolation and purification of the compounds of Formula (I), or separately by reacting the free base function with a suitable acid. Representative acid addition salts include hydrochloride, hydrobromide, sulfate, bisulfate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, toluenesulfonate, methanesulfonate, citrate, maleate, fumarate, succinate, tartrate, ascorbate, glucoheptonate, lactobionate, lauryl sulfate salts and the like. Representative alkali or alkaline earth metal salts include sodium, calcium, potassium, magnesium salts and the like. Examples of pharmaceutically acceptable, nontoxic amides of the compounds of Formula (I) include amides derived from C_1-C_6-alkyl carboxylic acids wherein the alkyl groups are straight- or branched-chain, aromatic carboxylic acids such as derivatives of benzoic acid and heterocyclic carboxylic acids, including furan-2-carboxylic acid or nicotinic acid. Amides of the compounds of Formula (I) may be prepared according to conventional methods and include amino acid and polypeptide derivatives of the amines of Formula (I).

As used herein, the term, "pharmaceutically acceptable carriers", means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of the materials that may serve as pharmaceutically acceptable carriers are sugars, such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene

glycol; polyols such as glycerin, sorbitol, mannitol and polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol and phosphate buffer solutions, as well as other non-toxic compatible substances used in pharmaceutical formulations. Wetting agents, emulsifiers and lubricants such as sodium lauryl-sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants may also be present in the composition, according to the judgment of the formulator. Examples of pharmaceutically acceptable antioxidants include water-soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfite, sodium metabisulfite, sodium sulfite, and the like; oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol and the like; and the metal chelating agents such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid and the like.

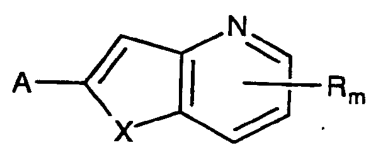
By a "therapeutically effective amount" of the cholinergic channel ligand agent, is meant a sufficient amount of the compound to treat cholinergically related disorders at a reasonable benefit/risk ratio applicable to obtain a desired therapeutic response. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidentally with the specific compound employed; and like factors well known in the medical arts. Total daily dose of the compounds of this invention administered to a host in single or divided doses may be in amounts as determined by the attending physician, typically, for example, in amounts of from about 0.001 to 100 mg/kg body weight daily and preferably 0.01 to 10 mg/kg/day. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

Examples of compounds falling within the scope of the present invention include:
2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
2-(2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
2-(1-methyl-2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)-5-methylfuro[3,2-b]pyridine;

2-(1-methyl-2-(S)-pyrrolidinyl)-5-methylfuro[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)-6-chlorofuro[3,2-b]pyridine;
2-(1-methyl-2-(S)-pyrrolidinyl)-6-chlorofuro[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)furo[2,3-c]pyridine;
2-(1-methyl-2-(S)-pyrrolidinyl)furo[2,3-c]pyridine;
2-(2-(S)-pyrrolidinyl)-5-chlorofuro[3,2-b]pyridine;
2-(1-methyl-2-(S)-pyrrolidinyl)-5-chlorofuro[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)-5-chlorofuro[2,3-b]pyridine;
2-(1-methyl-2-(S)-pyrrolidinyl)-5-chlorofuro[2,3-b]pyridine;
2-(hexahydro-1H-7a-pyrrolizinyl)furo[3,2-b]pyridine;
2-(hexahydro-1H-7a-pyrrolizinyl)-5-methylfuro[3,2-b]pyridine;
2-(hexahydro-1H-7a-pyrrolizinyl)furo[2,3-c]pyridine;
endo-2-(hexahydro-1H-3-(R)-pyrrolizidinyl)furo[2,3-c]pyridine;
exo-2-(hexahydro-1H-3-(S)-pyrrolizidinyl)furo[2,3-c]pyridine;
exo-2-(hexahydro-1H-3-(R)-pyrrolizidinyl)furo[2,3-c]pyridine;
endo-2-(hexahydro-1H-3-(S)-pyrrolizidinyl)furo[2,3-c]pyridine;
1-pyrrolidinylmethyl-(2-furo[3,2-b]pyridine);
5-chloro-2-(hexahydro-1H-7a-pyrrolizinyl)furo[3,2-b]pyridine;
2-(hexahydro-1H-7a-pyrrolizinyl)thieno[3,2-b]pyridine;
5,6-dichloro-2-(2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
5,6-dichloro-2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
2-(hexahydro-1H-7a-pyrrolizinyl)-4-methylthieno[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)-5-bromofuro[3,2-b]pyridine;
2-(2-(R)-pyrrolidinyl)-5-methylfuro[3,2-b]pyridine;
2-(1-methyl-2-(R)-pyrrolidinyl)-5-methylfuro[3,2-b]pyridine;
2-(2-(R)-pyrrolidinyl)-6-chlorofuro[3,2-b]pyridine;
2-(1-methyl-2-(R)-pyrrolidinyl)-5-chlorofuro[3,2-b]pyridine;
2-(2-(R)-pyrrolidinyl)-5-bromofuro[3,2-b]pyridine;
2-(2-(R)-pyrrolidinyl)furo[2,3-c]pyridine;
2-(2-(S)-pyrrolidinyl)-furo[3,2-b]pyridine-5-carboxylic acid;
2-(1-methyl-2-(S)-pyrrolidinyl)-6-trifluoromethylfuro[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)-5-aminofuro[3,2-b]pyridine;
2-(1-methyl-2-(S)-pyrrolidinyl)-5-(acetylamino)furo[3,2-b]pyridine;
2-(1-methyl-2-(S)-pyrrolidinyl)-5-(diethylamino)furo[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)-5-trichloromethylfuro[2,3-b]pyridine;
2-(2-(S)-pyrrolidinyl)-5-(methoxycarbonyl)furo[2,3-c]pyridine;
2-(1-methyl-2-(S)-pyrrolidinyl)-4-cyanofuro[2,3-c]pyridine; and
2-(1-methyl-2-(S)-pyrrolidinyl)-4-nitrofuro[2,3-c]pyridine;

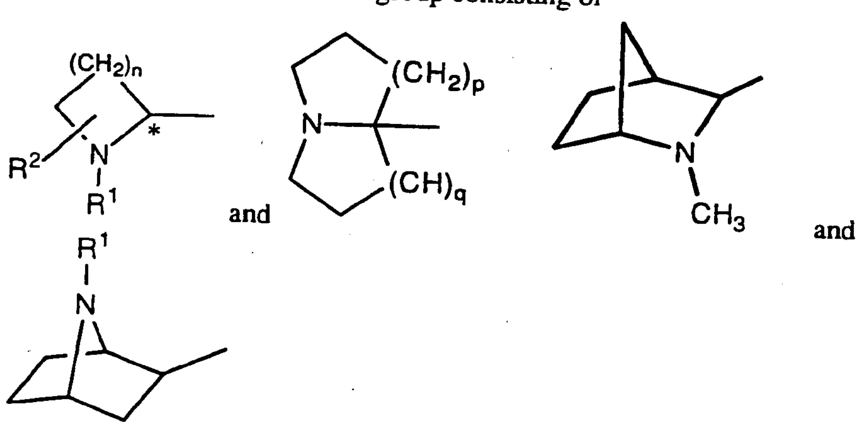
2-(2-(R)-pyrrolidinyl)-5-chlorofuro[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)furo[2,3-b]pyridine;
2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-c]pyridine;
2-(hexahydro-1H-7a-pyrrolizinyl)-5,6-dichlorofuro[3,2-b]pyridine;
5,6-dichloro-2-(2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
5,6-dichloro-2-(1-methyl-2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
2-((1R,4S)-2-aza-3-(S)-bicyclo[2.2.1]heptyl)-2-furo[3,2-b]pyridine;
2-((1R,4S)-2-aza-3-(S)-bicyclo[2.2.1]heptyl)-2-methyl-2-furo[3,2-b]pyridine;
2-((1R,4S)-2-aza-3-(S)-bicyclo[2.2.1]heptyl)-5-chloro-2-furo[3,2-b]pyridine;
2-((1R,4S)-2-aza-3-(S)-bicyclo[2.2.1]heptyl)-5-chloro-2-methyl-2-furo[3,2-b]pyridine;
2-((1R,4S)-2-aza-3-(S)-bicyclo[2.2.1]heptyl)-5,6-dichloro-2-furo[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)-6-bromofuro[3,2-b]pyridine;
6-bromo-2-(2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
6-bromo-2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
6-bromo-5-chloro-2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
6-bromo-5-chloro-2-(2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
6-bromo-5-chloro-2-(1-methyl-2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
7-chloro-2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
(±)-2-(7-aza-2-exo-bicyclo[2.2.1]heptyl)furo[3,2-b]pyridine; or
a pharmaceutically acceptable salt or prodrug thereof.

In a preferred embodiment of the present invention, there are provided compounds of formula (II)



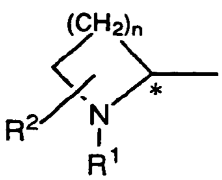
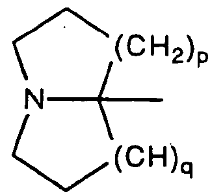
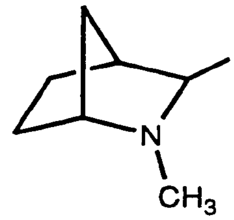
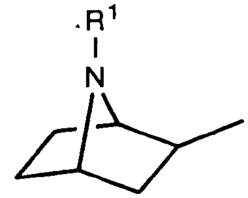
II

wherein A is selected from the group consisting of



Representative examples of the preferred compounds of the invention are:
2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
2-(2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
2-(1-methyl-2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)-5-methylfuro[3,2-b]pyridine;
2-(1-methyl-2-(S)-pyrrolidinyl)-5-methylfuro[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)-6-chlorofuro[3,2-b]pyridine;
2-(1-methyl-2-(S)-pyrrolidinyl)-6-chlorofuro[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)-5-chlorofuro[3,2-b]pyridine;
2-(1-methyl-2-(S)-pyrrolidinyl)-5-chlorofuro[3,2-b]pyridine;
5-chloro-2-(hexahydro-1H-7a-pyrrolizinyl)furo[3,2-b]pyridine;
2-(hexahydro-1H-7a-pyrrolizinyl)thieno[3,2-b]pyridine;
5,6-dichloro-2-(2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
5,6-dichloro-2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
2-(hexahydro-1H-7a-pyrrolizinyl)-4-methylthieno[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)-5-bromofuro[3,2-b]pyridine;
2-(2-(R)-pyrrolidinyl)-5-methylfuro[3,2-b]pyridine;
2-(1-methyl-2-(R)-pyrrolidinyl)-5-methylfuro[3,2-b]pyridine;
2-(2-(R)-pyrrolidinyl)-6-chlorofuro[3,2-b]pyridine;
2-(1-methyl-2-(R)-pyrrolidinyl)-5-chlorofuro[3,2-b]pyridine;
2-(2-(R)-pyrrolidinyl)-5-bromofuro[3,2-b]pyridine;
2-(2-(R)-pyrrolidinyl)-5-chlorofuro[3,2-b]pyridine;
2-(hexahydro-1H-7a-pyrrolizinyl)-5,6-dichlorofuro[3,2-b]pyridine;
5,6-dichloro-2-(2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
5,6-dichloro-2-(1-methyl-2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
6-bromo-2-(2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
6-bromo-2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
6-bromo-5-chloro-2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
6-bromo-5-chloro-2-(2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
6-bromo-5-chloro-2-(1-methyl-2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
7-chloro-2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
(±)-2-(7-aza-2-exo-bicyclo[2.2.1]heptyl)furo[3,2-b]pyridine; and
2-((1R,4S)-2-aza-3-(S)-bicyclo[2.2.1]heptyl)-2-methyl-2-furo[3,2-b]pyridine; or
a pharmaceutically acceptable salt or prodrug thereof.

In a particularly preferred embodiment of the present invention there is provided a compound of formula (II) above wherein A is selected from

 ,  ,  and  ,

wherein R is H, Br, Cl or C_1-C_4-alkyl, and R^2 is H.

Representative examples of the particularly preferred compounds of the present invention are:

2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
2-(2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
2-(1-methyl-2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)-5-methylfuro[3,2-b]pyridine;
2-(1-methyl-2-(S)-pyrrolidinyl)-5-methylfuro[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)-6-chlorofuro[3,2-b]pyridine;
2-(1-methyl-2-(S)-pyrrolidinyl)-6-chlorofuro[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)-5-chlorofuro[3,2-b]pyridine;
2-(1-methyl-2-(S)-pyrrolidinyl)-5-chlorofuro[3,2-b]pyridine;
5-Chloro-2-(hexahydro-1H-7a-pyrrolizinyl)furo[3,2-b]pyridine;
5,6-dichloro-2-(2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
5,6-dichloro-2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
2-(2-(R)-pyrrolidinyl)-5-methylfuro[3,2-b]pyridine;
2-(1-methyl-2-(R)-pyrrolidinyl)-5-methylfuro[3,2-b]pyridine;
2-(2-(R)-pyrrolidinyl)-6-chlorofuro[3,2-b]pyridine; and
2-(1-methyl-2-(R)-pyrrolidinyl)-5-chlorofuro[3,2-b]pyridine;
2-(2-(R)-pyrrolidinyl)-5-chlorofuro[3,2-b]pyridine;
2-(hexahydro-1H-7a-pyrrolizinyl)-5,6-dichlorofuro[3,2-b]pyridine;
5,6-dichloro-2-(2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
5,6-dichloro-2-(1-methyl-2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
7-chloro-2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
6-bromo-2-(2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
6-bromo-2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
6-bromo-5-chloro-2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
6-bromo-5-chloro-2-(2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
6-bromo-5-chloro-2-(1-methyl-2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
(±)-2-(7-aza-2-exo-bicyclo[2.2.1]heptyl)furo[3,2-b]pyridine; and
2-((1R,4S)-2-aza-3-(S)-bicyclo[2.2.1]heptyl)-2-methyl-2-furo[3,2-b]pyridine; or

a pharmaceutically acceptable salt or prodrug thereof.

Further included within the scope of the present invention are pharmaceutical compositions comprising one or more of the compounds of formula (I) prepared and formulated in combination with one or more non-toxic pharmaceutically acceptable carriers compositions, in the manner described below.

Compositions suitable for parenteral injection may comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propylene glycol, polyethylene glycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity may be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. Prevention of the action of microorganisms may be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example, sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical form may be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

If desired, and for more effective distribution, the compounds may be incorporated into slow-release or targeted-delivery systems, such as polymer matrices, liposomes, and microspheres. They may be sterilized, for example, by filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions, which may be dissolved in sterile water, or some other sterile injectable medium immediately before use.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier), such as sodium citrate or dicalcium phosphate, and additionally (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol and silicic acid; (b) binders, as for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose and acacia; (c) humectants, as for example, glycerol; (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates and sodium carbonate; (e) solution retarders, as for example paraffin; (f) absorption

accelerators, as for example, quaternary ammonium compounds; (g) wetting agents, as for example, cetyl alcohol and glycerol monostearate; (h) adsorbents, as for example, kaolin and bentonite; and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate or mixtures thereof. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules, using such excipients as lactose or milk sugar, as well as high molecular weight polyethylene glycols, and the like.

Solid dosage forms such as tablets, dragees, capsules, pills and granules may be prepared with coatings and shells, such as enteric coatings and others well known in this art. They may contain pacifying agents, and may also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions which may be used are polymeric substances and waxes.

The active compounds may also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan or mixtures of these substances, and the like.

Besides such inert diluents, these liquid dosage forms may also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

Compositions for rectal or vaginal administrations are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt in the rectum or vaginal cavity and release the active component.

Dosage forms for topical or transdermal administration of a compound of this invention further include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or transdermal patches. Transdermal administration via a transdermal patch is a particularly effective and preferred dosage form of the present invention. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservative, buffers or propellants as may be required. It is known that some agents may require special handling in the preparation of transdermal patch formulations. For example, compounds that are volatile in nature may require admixture with special formulating agents or with special packaging materials to assure proper dosage delivery. In addition, compounds which are very rapidly absorbed through the skin may require formulation with absorption-retarding agents or barriers. Ophthalmic formulations, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

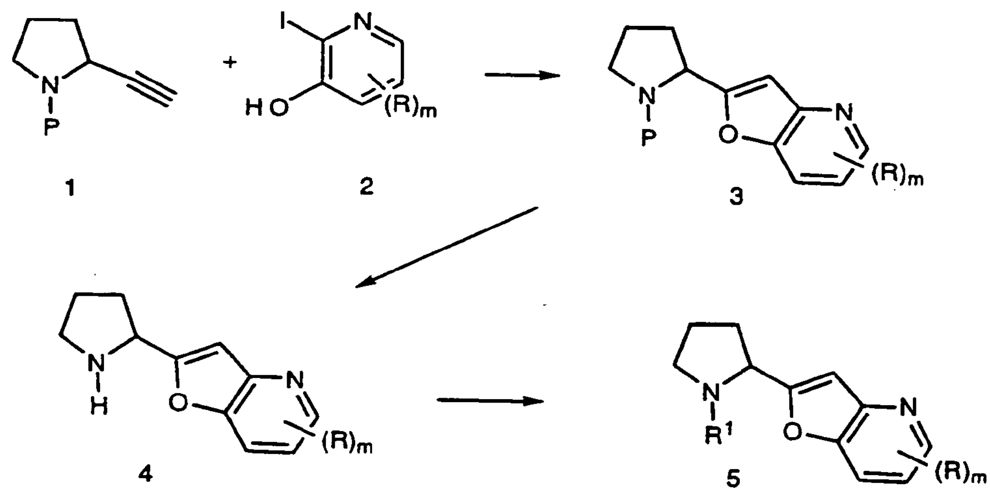
The present compounds may also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes may be used. The present compositions in liposome form may contain, in addition to the compounds of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and the phosphatidylcholines (lecithins), both natural and synthetic. Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N. Y., (1976), p 33 *et seq.*

In order to reduce unwanted peripherally mediated side-effects, it is advantageous, but not essential, to incorporate into the composition a peripherally acting anti-cholinergic such as N-methylscopolamine, N-methylatropine, propantheline, methantheline, or glycopyrrolate.

The compounds of the present invention may be synthesized as shown in reaction schemes I and II presented below using the reactions and techniques described in this section. The reactions are performed in a solvent appropriate to the reagents and materials employed are suitable for the transformation being effected. It is understood by those skilled in the art of organic synthesis that the functionality present on the heterocyclic ring and other portions of the molecule must be consistent with the chemical transformation proposed. This will, on occasion, necessitate judgment by the routineer as to the order of synthetic steps, protecting groups required, and deprotection conditions. Substituents on the starting materials may be incompatible with some of the reaction conditions required in some of the methods described, but alternative methods and substituents compatible with

the reaction conditions will be readily apparent to skilled practitioners in the art. The use of nitrogen-protecting groups is well known in the art for protecting amino groups against undesirable reactions during a synthetic procedure and many such protecting groups are known, cf, for example, T.H. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2nd edition, John Wiley & Sons, New York (1991).

Reaction Scheme 1

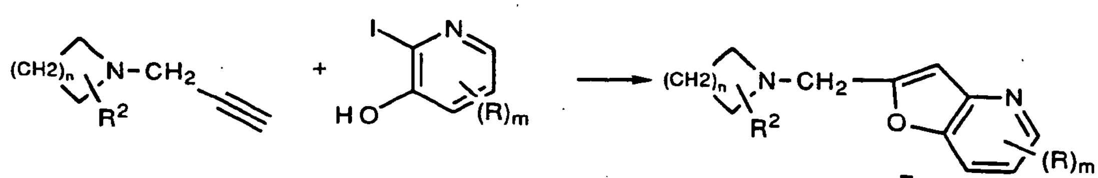


In accordance with Scheme 1 are prepared furo[3,2-b]pyridine compounds of Formula (I) wherein A is selected from group (a), R, R^1 and R^2 are as described above, X is O, Y^1 is N and Y^2 and Y^3 are CH. The process may be illustrated with the pyrrolidine series (n=2) thereof, in which an N-protected 2-acetylenylpyrrolidine starting material (1), wherein P is a N-protecting group, such as for example, BOC or CBZ, (which may be prepared from the corresponding imino-2-carboxylic acids according to known methods (Garvey, *et al.*, *J. Med. Chem.*, 35: 1550-1557, **1992**)) is reacted with an appropriate 2-iodo-3-hydroxypyridine (2), wherein R is as described above, in the presence of Pd, CuI and triethylamine at elevated temperature, to give the compound (3). (See Kundu, *et al.*, *J. Chem. Soc. Chem. Comm.*, **1992**: 41 for analogous preparation of benzofurans). The protecting group P may then be removed by standard methods to give compound (4), i.e., compounds of formula (I) wherein R^1 is H. Compound (4) may be converted into compounds (5), i.e., compounds of formula (I) wherein R^1 is C_1-C_3-alkyl by reaction with the appropriate aldehyde under reducing conditions, for example, in the presence of H_2 and a catalyst such as Pd/C. The process of Scheme 1 is equally applicable to compounds of the series wherein n is 1 or 3, to give compounds analogous to compounds (4) and (5), i.e., compounds of formula (I) wherein A is (a) and n is 1 or 3.

Alternately, for compounds of Formula (I) wherein X is S, compounds are prepared by appropriate modifications of the above schemes for X = O. The appropriate precursor o-halo-hydroxyheterocycles are converted to the corresponding o-halo-mercaptoheterocycles

by reaction with a diakylthiocarbamyl chloride, for example diethyl thiocarbamyl chloride, followed by heating to effect rearrangement to the thiocarbamate, followed by hydrolysis (Kwart and Evans, *J. Org. Chem.*, 31: 410, **1966**; Newman and Karnes, *Org. Syn.*, 51:139, **1971**). The resultant o-halo-mercaptoheterocycles are then allowed to react with the acetylene compound (1) under copper catalysis (optionally in the presence of palladium) at elevated temperature to afford thieno-fused heterocycles (cf. Malte and Castro, *J. Am. Chem. Soc.*, 89: 6770, **1967**). Such reactions may be applied to give the desired starting materials wherein O is replaced by S for the compounds described in the following schemes, also.

Reaction Scheme 2



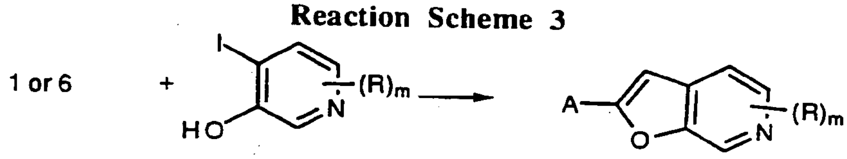
In accordance with Scheme 2 are prepared furo[3,2-b]pyridine compounds of Formula (I) wherein A is selected from group (b), R^2 is as described above, X is O, Y^1 is N and Y^2 and Y^3 are CH. The process may be illustrated with the pyrrolidine series (n=2) thereof, in which a 1-(3-propynyl)pyrrolidine starting material (6) (which may be prepared by reaction of the appropriately substituted pyrrolidine with 3-bromopropyne under basic conditions; see, for example, Biehl and DiPierro, *J. Am. Chem. Soc.*, 80:4609-4614, **1958**). The compound (6) is reacted with an appropriate 2-iodo-3-pyridinol (2), wherein R is as described above, in the presence of Pd, CuI and triethylamine at elevated temperature, to give the compound (7). The process of Scheme 2 is equally applicable to compounds of the series wherein n is 1 or 3, to give compounds analogous to compound (7), i.e., compounds of formula (I) wherein A is (b) and n is 1 or 3.

The 2-iodo-3-pyridinols of Schemes 1 and 2 may be prepared by direct selective iodination of the corresponding pyridinols (e.g., Koch and Schnatterer, *Synthesis*, **1990**:497). Alternately, 3-pyridinols with substituents in the 4-position can be prepared by selective lithiation of 3-pyridinol, O-protected with an ortho-directing moiety, e.g. methoxymethyl , diethylcarbamoyl, and the like (see Beak and Snieckus, *Acc. Chem. Res.*, 15:306-312, **1982**). Alternately, 3-hydroxypyridines with substituents in other required positions can be prepared from the corresponding 3-aminopyridines under diazotizing conditions. Where appropriate, the 3-aminopyridines can be obtained by reduction of the corresponding 3-nitropyridine or by rearrangement of the 3-carboxylic acid or 3-carboxamide using the Hoffman, Curtius, or Schmidt rearrangements which are well-

known in the art. In addition, 3-hydroxypyridines can be obtained by oxidation of an appropriate 3-lithio or magnesiopyridine with molecular oxygen, oxaziridines, or peroxides (see, for example, Taddei and Ricci, *Syn. Comm.*, **1986**:633-635), or alternately peroxide oxidation of a pyridyl-3-dialkylborate, which can be obtained by reaction of a trialkyl borate with the appropriate 3-lithio- or magnesiopyridine (cf. Lawesson and Yang, *J. Am. Chem. Soc.*, 81:4320, **1959**, and/or Hawthorne, *J. Org. Chem.*, 22:1001, **1957**).

In an alternate procedure, the reactions of Scheme 2 may be performed with the analogous mercaptopyridine, prepared as described for Scheme 1 above, to give the thieno[3,2-b]pyrimidine compounds of Formula (I), wherein X is a S atom.

Reaction Scheme 3



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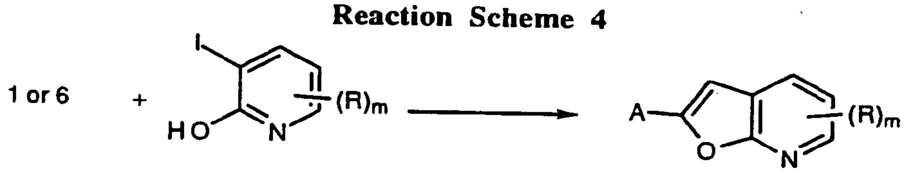
In accordance with Scheme 3 are prepared furo[2,3-c]pyridine compounds of Formula (I) wherein A is selected from (a) or (b) above, R, R^1 and R^2 are as described above, X is O, Y^1 is CH, Y^2 is N and Y^3 is CH. The acetylene-substituted starting material (1) or (6) is reacted with an appropriate 4-iodo-3-hydroxypyridine (9), wherein R is as described above, in the presence of Pd, CuI and triethylamine at elevated temperature, to give the compound (10). The requisite 4-iodo-3-hydroxypyridines are generally available using the techniques mentioned above together with selective 4-iodination of 3-hydroxypyridines (cf. Winkle and Ronald, *J. Org. Chem.*, 47:2101, **1982**). In a further alternate procedure, the reactions of Scheme 3 may be performed with the analogous mercaptopyridine, prepared as described for Scheme 1 above, to give the thieno[2,3-c]pyrimidine compounds of Formula (I), wherein X is a S atom.

Reaction Scheme 4

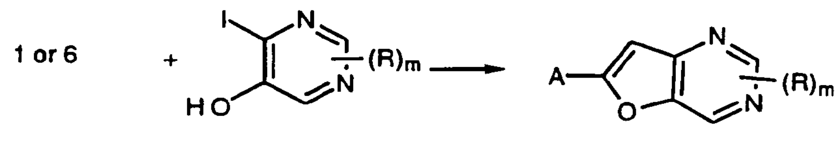


11 12

In accordance with Scheme 4 are prepared furo[2,3-b]pyridine compounds of Formula (I) wherein A is selected from (a) or (b) above, R, R^1 and R^2 are as described above, X is O, Y^1 and Y^2 are CH and Y^3 is N. The acetylene-substituted starting material (1) or (6) is reacted with an appropriate 3-iodo-2-hydroxypyridine (11), wherein R is as described above, in the presence of Pd, CuI and triethylamine at elevated temperature, to

give the compound (12). The requisite 3-iodo-2-hydroxypyridines are generally available using the techniques mentioned above for synthesis of selectively substituted 3-hydroxypyridines. For example, the requisite 3-iodo-2-hydroxypyridines can be obtained by ortho iodination of the appropriate 2-hydroxypyridine. In a further alternate procedure, the reactions of Scheme 4 may be performed with the analogous mercaptopyridine, prepared as described for Scheme 1 above, to give the thieno[2,3-b]pyrimidine compounds of Formula (I), wherein X is a S atom.

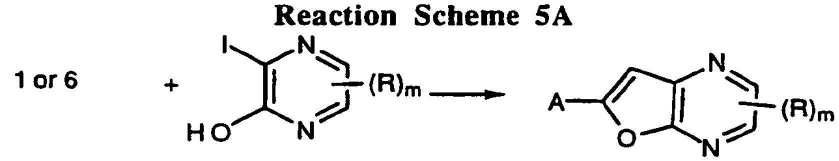
Reaction Scheme 5



13 14

In accordance with Scheme 5 are prepared furo[3,2-d]pyrimidine compounds of Formula (I) wherein A is selected from (a) or (b) above, R, R^1 and R^2 are as described above, X is O, Y^1 is N, Y^2 is N and Y^3 is CH. The acetylene-substituted starting material (1) or (6) is reacted with an appropriate 4-iodo-5-hydroxypyrimidine (13), wherein R is as described above, in the presence of Pd, CuI and triethylamine at elevated temperature, to give the compound (14). The requisite 4-iodo-5-hydroxypyrimidine compounds are generally available using the techniques mentioned above for synthesis of selectively substituted 3-hydroxypyridines. For example, the requisite 4-iodo-5-hydroxypyrimidine can be obtained by ortho iodination of the appropriate 5-hydroxypyrimidine. In a further alternate procedure, the reactions of Scheme 5 may be performed with the analogous mercaptopyridine, prepared as described for Scheme 1 above, to give the thieno[3,2-d]pyrimidine compounds of Formula (I), wherein X is a S atom.

Reaction Scheme 5A

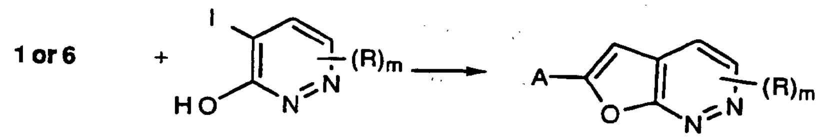


13A 14A

In accordance with Scheme 5A are prepared furo[2,3-b]pyrimidine compounds of Formula (I) wherein A is selected from (a) or (b) above, R, R^1 and R^2 are as described above, X is O, Y^1 is N, Y^2 is N and Y^3 is CH. The acetylene-substituted starting material (1) or (6) is reacted with an appropriate 3-iodo-2-hydroxypyrimidine (13A), wherein R is as

described above, in the presence of Pd, CuI and triethylamine at elevated temperature, to give the compound (14A). The requisite 3-iodo-2-hydroxypyrimidine compounds are generally available using the techniques mentioned above for synthesis of selectively substituted 2-hydroxypyridines. For example, the requisite 3-iodo-2-hydroxypyrimidine can be obtained by ortho iodination of the appropriate 2-hydroxypyrimidine. In a further alternate procedure, the reactions of Scheme 5A may be performed with the analogous mercaptopyridine, prepared as described for Scheme 1 above, to give the thieno[2,3-b]pyrimidine compounds of Formula (I), wherein X is a S atom.

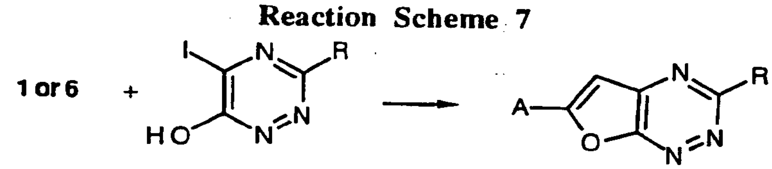
Reaction Scheme 6



15 16

In accordance with Scheme 6 are prepared furo[2,3-c]pyridazine compounds of Formula (I) wherein A is selected from (a) or (b) above, R, R^1 and R^2 are as described above, X is O, Y^1 is CH, and Y^2 and Y^3 are N. The acetylene-substituted starting material (1) or (6) is reacted with an appropriate 4-iodo-3-hydroxypyridazine (15), wherein R is as described above, in the presence of Pd, CuI and triethylamine at elevated temperature, to give the compound (16). The requisite 4-iodo-3-hydroxypyridazine compounds are generally available using the techniques mentioned above for synthesis of selectively substituted 3-hydroxypyridines. For example, the requisite 4-iodo-3-hydroxypyridazine can be obtained by ortho iodination of the appropriate 5-hydroxypyridazine. In a further alternate procedure, the reactions of Scheme 6 may be performed with the analogous mercaptopyridine, prepared as described for Scheme 1 above, to give the thieno[2,3-c]pyridazine compounds of Formula (I), wherein X is a S atom.

Reaction Scheme 7



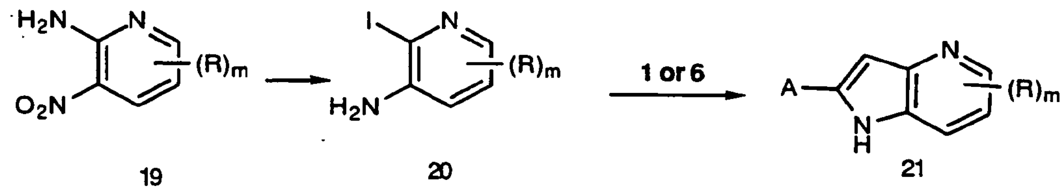
17 18

In accordance with Scheme 7 are prepared furo[3,2-e]triazine compounds of Formula (I) wherein A is selected from (a) or (b) above, R, R^1 and R^2 are as described above, X is O, Y^1 is CH, Y^2 is N and Y^3 is N . The acetylene-substituted starting material (1) or (6) is reacted with an appropriate 5-iodo-6-hydroxytriazine (17), wherein R is as

described above, in the presence of Pd, CuI and triethylamine at elevated temperature, to give the compound (18). The requisite 5-iodo-6-hydroxytriazine compounds are generally available using the techniques mentioned above for synthesis of selectively substituted 3-hydroxypyridines. For example, the requisite 5-iodo-6-hydroxytriazine can be obtained by ortho iodination of the appropriate 5-hydroxytriazine.

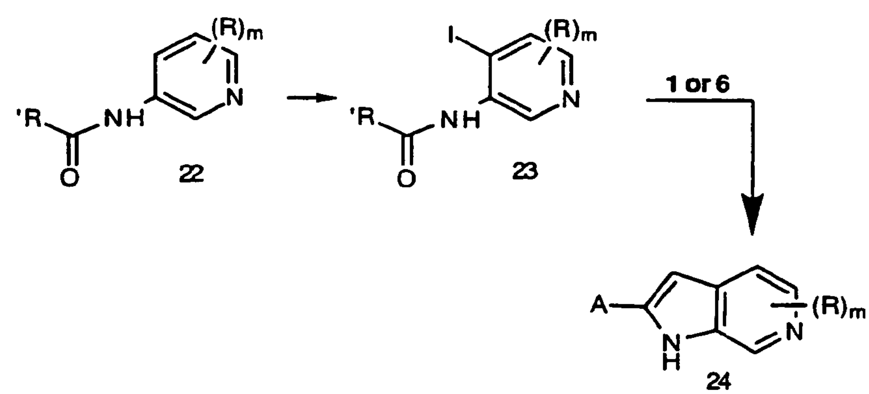
Alternately, this reaction may be performed with the analogous mercaptopyrimidine, prepared as described for Scheme 1 above, to give the thieno[3,2-e]triazine compounds of Formula (I), wherein X is a S atom.

Reaction Scheme 8



In accordance with Scheme 8 are prepared pyrrolo[3,2-b]pyridine compounds of Formula (I) wherein A is selected from (a) or (b) above, R, R^1 and R^2 are as described above, X is NH, Y^1 is N and Y^2 and Y^3 are CH. A starting material amino-nitro pyridine (19) is reacted with NaNO2 and HI to replace the amino group with an iodo group, then with iron and acetic acid to reduce the nitro group to an amino group and give the compound (20). Compound 20 is then reacted with compound 1 or 6 in the presence of Pd, CuI and triethylamine at elevated temperature, as described above, to give the compound (21).

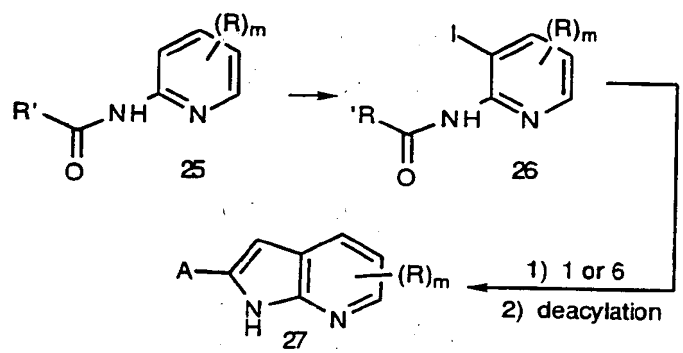
Reaction Scheme 9



In accordance with Scheme 9 are prepared pyrrolo[2,3-c]pyridine compounds of Formula (I) wherein A is selected from (a) or (b) above, R, R^1 and R^2 are as described above, X is NH, Y^1 and Y^3 are CH and Y^2 is N. A protected aminopyridine compound

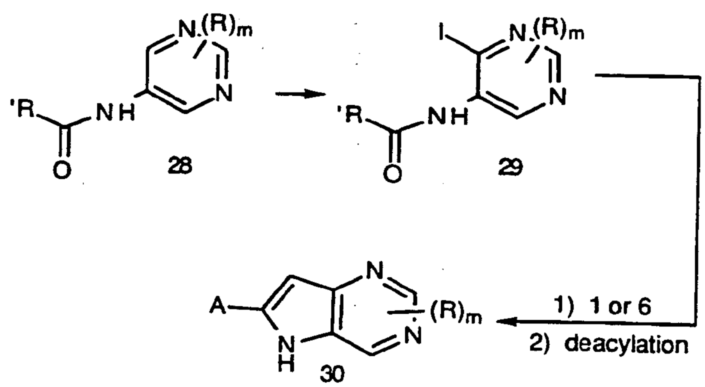
starting material (22) is reacted with a strong base, such as t-butyllithium, and free iodine to give the iodinated compound (23). Compound (23) is then reacted with compound (1) or (6) in the presence of Pd, CuI and triethylamine at elevated temperature, as described above, to give the compound (24).

Reaction Scheme 10



In accordance with Scheme 10 are prepared pyrrolo[2,3-b]pyridine compounds of Formula (I) wherein A is selected from (a) or (b) above, R, R^1 and R^2 are as described above, X is NH, Y^1 and Y^2 are CH and Y^3 is N. A protected aminopyridine compound starting material (25) is reacted with a strong base, such as t-butyllithium, and free iodine to give the iodinated compound (26). Compound (26) is then reacted with compound (1) or (6) in the presence of Pd, CuI and triethylamine at elevated temperature, as described above, then deacylated by standard methods to give the compound (27).

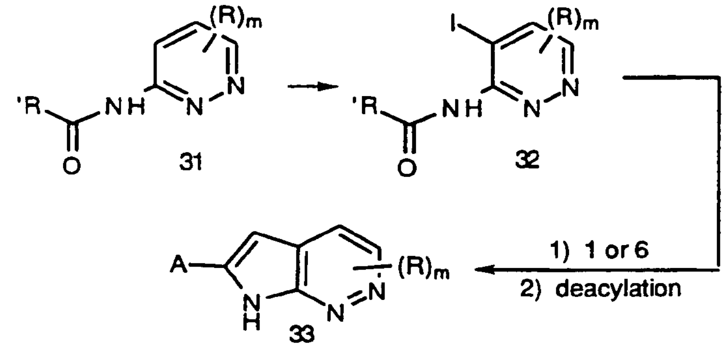
Reaction Scheme 11



In accordance with Scheme 11 are prepared pyrrolo[3,2-d]pyrimidine compounds of Formula (I) wherein A is selected from (a) or (b) above, R, R^1 and R^2 are as described above, X is NH, Y^1 and Y^2 are N, and Y^3 is CH . A protected aminopyrimidine compound starting material (28) is reacted with a strong base, such as t-butyllithium, and free iodine to

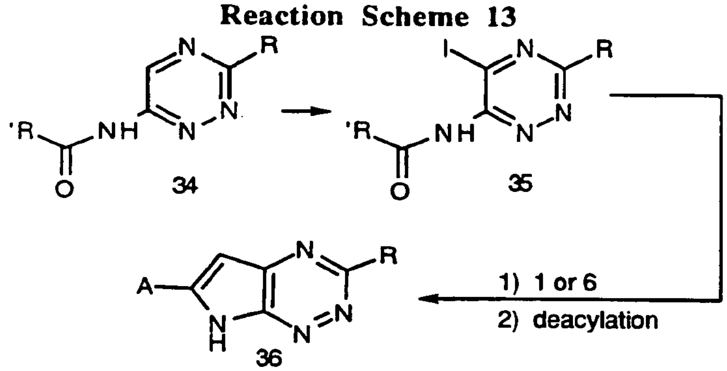
give the iodinated compound (29). Compound (29) is then reacted with compound (1) or (6) in the presence of Pd, CuI and triethylamine at elevated temperature, as described above, then deacylated by standard methods to give the compound (30).

Reaction Scheme 12



In accordance with Scheme 12 are prepared pyrrolo[2,3-c]pyridazine compounds of Formula (I) wherein A is selected from (a) or (b) above, R, R^1 and R^2 are as described above, X is NH, Y^1 is CH, and Y^2 and Y^3 are N. A protected aminopyridazine compound starting material (31) is reacted with a strong base, such as t-butyllithium, and free iodine to give the iodinated compound (32). Compound (32) is then reacted with compound (1) or (6) in the presence of Pd, CuI and triethylamine at elevated temperature, as described above, then deacylated by standard methods to give the compound (33).

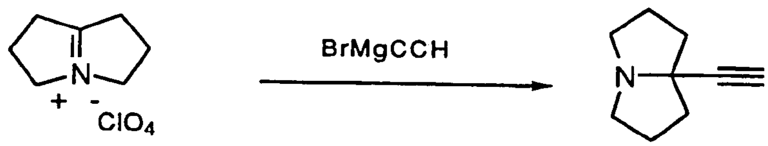
Reaction Scheme 13



In accordance with Scheme 13 are prepared pyrrolo[3,2-e]triazine compounds of Formula (I) wherein A is selected from (a) or (b) above, R, R^1 and R^2 are as described above, X is NH, Y^1 is CH, and Y^2 and Y^3 are N. A protected aminotriazine compound starting material (34) is reacted with a strong base, such as t-butyllithium, and free iodine to give the iodinated compound (35). Compound (35) is then reacted with compound (1) or

(6) in the presence of Pd, CuI and triethylamine at elevated temperature, as described above, then deacylated by standard methods to give the compound (36).

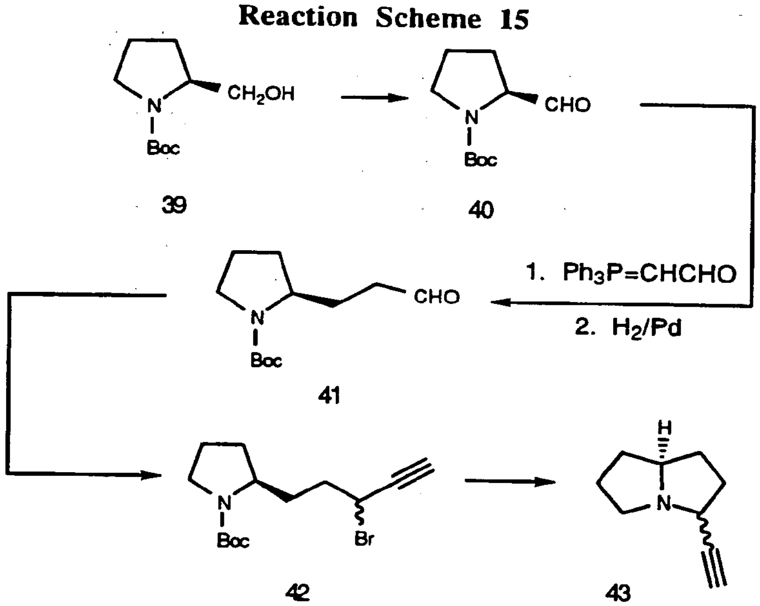
Reaction Scheme 14



37 38

In accordance with Scheme 14 is prepared the 7a-ethynylpyrrolizidine starting material for compounds of Formula (I) wherein A is selected from option (c). The starting material pyrrolizidinium compound (prepared according to the procedure of Miyano *et al.*, *Synthesis*, 1978:701-2) is reacted with the ethynyl magnesium bromide under appropriate Grignard conditions to give the compound (38). Compound 38 may be substituted for compounds (1) or (6) in any of Schemes 1-13 above to give the desired compound of Formula (I).

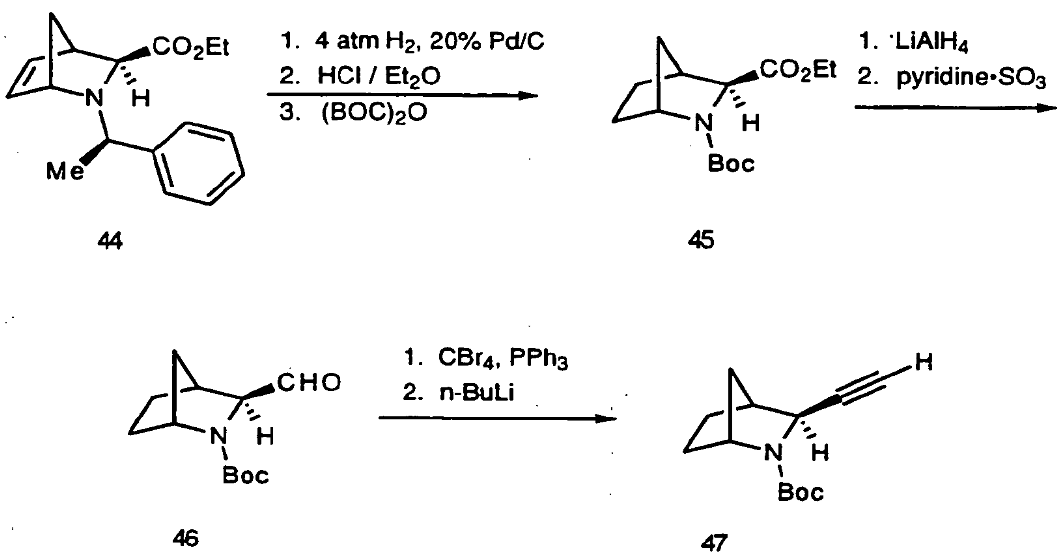
Reaction Scheme 15



In accordance with Scheme 15 is prepared the 3-ethynylpyrrolizidine starting material for compounds of Formula (I) wherein A is selected from option (d). The protected prolinol (39) is converted to the aldehyde compound (40) by reaction with triethylamine and pyridine•sulfur trioxide complex in DMSO. Compound (40) is reacted with (triphenylphosporanylidene)acetaldehyde, followed by reduction of the intermediate

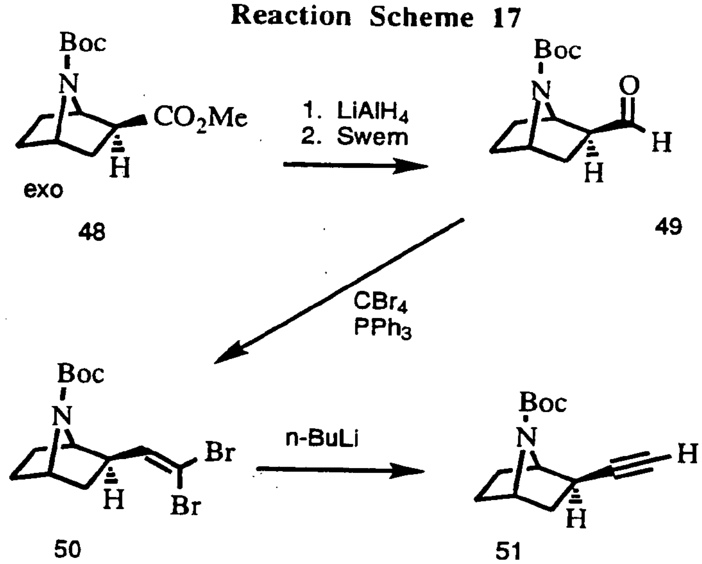
with H_2 over a Pd/C catalyst to give the extended aldehyde compound (41). Compound (41) is subsequently reacted with, for example, ethynyl magnesium bromide and the intermediate is reacted with triphenylphosphine dibromide to give compound (42). Compound 42 is treated with HCl in a polar organic solvent, such as ethanol, for example to give the 3-substituted pyrrolizidine compound (43). Compound (43) may be substituted for compounds (1) or (6) in any of Schemes 1-13 above to give the desired compound of Formula (I).

Reaction Scheme 16



In accordance with Scheme 16 is prepared the ethynyl substituted 2-azabicyclo[2.2.1]heptane starting material for compounds of Formula (I) wherein A is selected from option (e). Compound (44) (prepared according to the procedure of Stella et al., Tetrahedron Lett., 31:2603 (1990)) is deprotected by hydrogenolysis over Pd/C, then reprotected by treatment with di-t-butyldicarbonate to give the BOC-protected compound (45). Compound (45) is reduced with LAH to an intermediate alcohol, which is then oxidized to obtain the aldehyde (46). Compound (46) is treated with PPh_3 and CBr_4 to give an intermediate dibromoalkene (not shown), which is then converted to the alkyne (47) by treatment with an alkyllithium compound. Compound (47) may be substituted for compounds (1) or (6) in any of Schemes 1-13 above to give the desired compound of Formula (I).

Reaction Scheme 17



In accordance with Scheme 17 is prepared the ethynyl substituted 7-azabicyclo[2.2.1]heptane starting material for compounds of Formula (I) wherein A is selected from option (f). Compound (48) (prepared according to the procedure of Hernandez *et al.*, *J. Org. Chem.*, 60:2683-2691 (**1995**)) is reduced with LAH to an intermediate alcohol, which is then oxidized under Swern conditions to obtain the aldehyde (49). Compound (49) is treated with PPh_3 and CBr_4 to give the dibromoalkene (50), which is then converted to the alkyne (51) by treatment with an alkyllithium compound. Compound (51) may be substituted for compounds (1) or (6) in any of Schemes 1-13 above to give the desired compound of Formula (I).

It should be noted that compounds of Formula (I) wherein R is C_1-C_4-alkyl, Br, Cl, F, CF_3 or CCl_3 may be conveniently prepared by starting with the appropriately substituted compounds 2, 9, 11, 13, 13A, 15, 17, 20, 23, 26, 29, 32 or 35, which, if necessary, may be prepared by common techniques from the unsubstituted pyridine, pyrimidine or pyrazine starting materials or other commercially available derivatives thereof. Preparation of additional iodohydroxyheterocycles may be carried out by selective electrophilic aromatic substitution reactions upon the corresponding hydroxyheterocycles. In the above selective electrophilic substitution reactions, occasionally it may be necessary or desirable to achieve the desired position of substitution by blocking a more readily substituted position with a blocking and/or directing group, e.g. chloro or nitro, which can subsequently be removed by, respectively, reduction or a reduction/diazotization/reduction sequence. Alternately, a bromo- or chloro-substituent on an intermediate substituted pyridine a fully assembled furopyridine or related heterocycle which has been constructed by way of the methods described above can be converted to other substituents. For example, by treating a

compound of Formula (I) wherein R is Br with NH_3, optionally with catalysis by copper salts, under heat and pressure, compounds of Formula (I) wherein R is NH_2 may be prepared. Further treatment of compounds of Formula (I) wherein R is NH_2 with $NaNO_2$ and CuCN allows the preparation of compounds of Formula (I) wherein R is CN. As a further example, amino may be oxidized with H_2SO_4 and H_2O_2 to nitro, or carboxamide may be dehydrated to cyano. Cyano groups may be treated with the appropriate alcohol in the presence of a strong acid to prepare compounds of Formula (I) wherein R is COO-C_1-C_4-alkyl. Further hydrolysis of these esters with mild base gives the compounds of Formula (I) wherein R is COOH. Or compounds of Formula (I) wherein R is NH_2 may be N-acylated by the appropriate C_1-C_4-acyl chloride to give compounds of Formula (I) wherein R is NH-CO-C_1-C_4-alkyl. Further, compounds of Formula (I) wherein R is NH_2 may by alkylated to give the compounds of Formula (I) wherein R is NR^1R^1. Also, bromo- or chloro-substituted compounds may be replaced with alkyl or alkenyl in reactions moderated by transition metals, e.g., palladium or nickel. Such alternate procedures as may be required are well known to those skilled in the art, and such alternate substituents are considered to be within the scope of the invention. Appropriate precursors to compounds 13, 13A, 15, 17, 29, 32 and 35 may also be prepared by ring-closure reactions of appropriately substituted acyclic compounds, such reactions being well known to those skilled in the art.

A. Protocol For Determination of Nicotinic Cholinergic Channel Receptor Binding Potencies of Ligands

Binding of [^{3}H]-cytisine ([^{3}H]-CYT) to nicotinic receptors was accomplished using crude synaptic membrane preparations from whole rat brain (Pabreza *et al.*, *Molecular Pharmacol.*, **1990**, 39:9). Washed membranes were stored at -80°C prior to use. Frozen aliquots were slowly thawed and resuspended in 20 volumes of buffer (containing: 120 *mM* NaCl, 5 *mM* KCl, 2 *mM* $MgCl_2$, 2 *mM* $CaCl_2$ and 50 *mM* Tris-Cl, pH 7.4 @4°C). After centrifuging at 20,000x g for 15 minutes, the pellets were resuspended in 30 volumes of buffer. Homogenate (containing 125-150 µg protein) was added to triplicate tubes containing concentrations of test compound and [^{3}H]-CYT (1.25 *nM*) in a final volume of 500 µL. Samples were incubated for 60 minutes at 4°C, then rapidly filtered through Whatman GF/B filters presoaked in 0.5% polyethylimine using 3 x 4 mL of ice-cold buffer. The filters were counted in 4 mL of Ecolume® (ICN). Nonspecific binding was determined in the presence of 10 µM (-)-nicotine and values were expressed as a percentage of total binding. IC_{50} values were determined with the RS-1 (BBN) nonlinear least squares curve-fitting program and IC_{50} values were converted to Ki values using the Cheng and Prusoff correction (Ki=IC_{50}/(1+[ligand]/Kd of ligand). Alternately, data were expressed as a percentage of the total specific binding. The results (shown in Table 1) suggest that the

compounds of the present invention have high affinity for the neuronal nicotinic cholinergic channel receptor.

In Vitro Determination of Neuronal Nicotinic Receptor Binding Potencies

For the purpose of identifying compounds as cholinergic agents which are capable of interacting with cholinergic channel receptors in the brain, a ligand-receptor binding assay was carried out as the initial screen. Compounds of the present invention were effective at interacting with neuronal nicotinic cholinergic receptors as assayed for their ability to displace radioligand from neuronal nicotinic cholinergic channel receptors labeled with [^{3}H]-cytisine ([^{3}H]-CYT).

The ability of the compounds of the invention to interact with cholinergic channel receptors and thereby to activate or inhibit synaptic transmission can be demonstrated *in vitro* using the following protocol.

B. Protocols for the Determination of Functional Effects of Cholinergic Channel Receptor Ligands on Synaptic Transmission

Cells of the IMR-32 human neuroblastoma clonal cell line (ATCC, Rockville, MD) were maintained in a log phase of growth according to established procedures (Lukas, 1993). Experimental cells were seeded at a density of 500,000 cells/mL into a 24-well tissue culture dish. Plated cells were allowed to proliferate for at least 48 hours before loading with 2 µCi/mL of $^{86}Rb^+$ (35 Ci/mmol) overnight at 37°C. The $^{86}Rb^+$ efflux assays were performed according to previously published protocols (Lukas, R.J., *J. Pharmacol. Exp. Ther.*, 265: 294-302, **1993**) except serum-free Dulbecco's Modified Eagle's Medium was used during the $^{86}Rb^+$ loading, rinsing, and agonist-induced efflux steps.

Cells of the K177 cell line, resulting from stable transfection of the human embryonic kidney (HEK) 293 cell line with the cDNA of the α4 and β2 nicotinic acetylcholine subunits (Gopalakrishnan, et al, *J. Pharmacol. Expt. Ther.* **1996**, 276, 289-297), were maintained in a log phase of growth according to established procedures (Gopalakrishnan, et al., *loc. cit.*). The cells were plated onto poly-lysine coated 24-well Costar plates (Cambridge, MA) at a density of 250,000 cells/well. When confluent, the cells were loaded with $^{86}Rb^+$ and agonist-induced efflux was assessed as reported above for IMR-32 cells.

Maximal responses (reported as percent relative to the response elicited by 100 µM (S)-nicotine) are shown for selected compounds of the invention. The inhibition data (given for other selected compounds) reflect inhibition of the efflux elicited by 100 µM (S)-nicotine at the indicated concentration. The results (also shown in Table 1) suggest that selected compounds of the present invention either activate or inhibit the initial ion flux aspects of synaptic transmission mediated by neuronal nicotinic acetylcholine receptors. This finding

is in agreement with the results of others who have linked dopamine release, which is dependent upon the ion flux in synaptic transmission, to binding at nicotinic receptors (cf., for example, Lippiello and Caldwell, U.S.Patent 5,242,935, issued Sept. 7, 1993; Caldwell and Lippiello, U.S.Patent 5,248,690, issued Sept. 28, 1993; and Wonnacott *et al.*, Prog. Brain Res., 79: 157-163 (**1989**)).

Table 1
Binding to Neuronal Nicotinic Receptors
and Activation or Inhibition of Neuronal Nicotinic
Cholinergic Channels in K177 or IMR-32 Cells

Ex. No	Binding (nM)	K177 % max	K177 % Inhibition @10 mM	IMR-32 % max	IMR-32 % Inhibition @30 mM
1	2.7	79		7	16
2	76				
3	4.1			58	
4	17.5				
5	355				
6	4.7	68		14	
7	878				
8	27	3	45	7	
9	250			83	
10	207				
11	58				
12	4.1	41		11	
13	4440				
14	181				
15	0.45			43	
16	5.8	109		0	
17	88				
18	38				55
19	3950				
20	397				
21	3300			0	50
22	113				
23	0.62				
24	2	14	60		
25	103				
26	0.66	6	53		
27	27				
28	4.8				
29	6.8	0	28		
30	101				
31	9.8	13	41		
32	54				
33	200				
34	1710				
35	1.1	61			
36	611				
37	1760				
38	0.33				
38	1.1	39		4	43 (@10 mM)
40	32				

41	81				
42	4.7				
43	453				
44	5				
45	205				
46	468				
47	38				
48	1.3	0		3	0
49	2.6				
50	46				
51	443				
52	0.86	36		70	

The following examples will serve to further illustrate preparation of the novel compounds of the invention and their biological activity. They are not to be read as limiting the scope of the invention as it is defined by the appended claims.

Thin-layer chromatography (TLC) was performed on 0.25 mm E. Merck precoated silica gel plates (60 F-254). Flash chromatography was performed on 200-400 mesh silica gel (E. Merck), and column chromatography was performed on 70-230 mesh silica gel (E. Merck).

The following abbreviations are used: THF for tetrahydrofuran, DMF for N, N-dimethylformamide, D_2O for deuterium oxide, $CDCl_3$ for deuterochloroform, DMSO-d_6 for deuterodimethylsulfoxide, BOC for *tert*-butyloxycarbonyl, CBZ for benzyloxycarbonyl, Bn for benzyl, Ms for methanesulfonyl, PAW for pyridine/acetic acid/water (20:6:11), DCC for dicyclohexylcarbodiimide, DIBALH for diisobutylaluminum hydride, DIEA for diisopropylethylamine, DPPA for diphenylphosphororyl azide, DME for 1,2-dimethoxyethane, EDCI for 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride, EtOH for ethanol, IBCF for isobutyl chloroformate, HOAc for acetic acid, HOBT for 1-hydroxybenzotriazole, LAH for lithium aluminum hydride, NH_4OAc for ammonium acetate, dppp for 1,3-bis(diphenylphosphino)propane; NMM for N-methylmorpholine, TEA for triethylamine, THF for tetrahydrofuran.

Example 1

Preparation of 2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine dihydrochloride

1a. N-BOC-(S)-prolinal

N-BOC-(S)-proline was reduced to N-BOC-(S)-prolinol by treatment with diborane as described by K.E. Rittle *et al.* (*J. Org. Chem.*, 47:3016 (**1982**)). N-t-butyloxycarbonyl-(S)-prolinol was then oxidized to N-t-butyloxycarbonyl-(S)-prolinal by

treatment with sulfur trioxide-pyridine complex as described by Y. Hamada and T. Shioiri (*Chem. Pharm. Bull*, 5:1921 (**1982**)).

1b. 2(S)-(2,2-Dibromoethenyl)-N-t-butyloxycarbonylpyrrolidine

At room temperature and under nitrogen, triphenylphosphine (13.0 g, 49.5 mmol), zinc dust (2.16 g, 33.0 mmol) and carbon tetrabromide (11.0 g, 33.0 mmol) were added to dichloromethane (80 mL). After stirring for 5 minutes, a solution of N-t-butyloxycarbonyl-(S)-prolinal (3.29 g, 16.5 mmol) in dichloromethane (25 mL) was added. The reaction was slightly exothermic. After stirring for 1 hour, the reaction mixture was diluted with ethyl acetate/hexane (1:1) and filtered through basic alumina. The filter cake was then washed with a mixture of dichloromethane/ethyl acetate/hexane (1:1:1). The filtrate was concentrated *in vacuo*, and the residue was taken up in ethyl acetate/hexane (1:1). The resulting precipitate was filtered, and the filtrate was concentrated. The residual oil was subjected to flash chromatography using ethyl acetate/hexane (1:6.5 to 1:5) as the eluant. The resultant pure solid product was isolated in 91% yield (5.31 g): mp 65-66 °C; $[\alpha]_D^{23}$ +20.1 (c 1.10, MeOH); ^{1}H NMR (DMSO-d_6, 70 °C, 300 MHz) δ 6.57 (d, J=8.1 Hz, 1H), 4.26 (ddd, J=7.9, 7.9, 4.9 Hz, 1H), 3.30 (m, 2H), 2.11 (m, 1H), 1.72-1.92 (m, 2H), 1.65 (m, 1H), 1.40 (s, 9H); MS m/e 354 $(M+H)^+$; Anal. Calcd for $C_{11}H_{17}Br_2NO_2$: C, 37.21; H, 4.83; N, 3.95. Found: C, 37.45; H, 4.85; N, 3.97.

1c. 1-BOC-2-(S)-ethynylpyrrolidine

A solution of the compound of step 1b above (27.1 g, 76.3 mmol) and THF (550 mL) was cooled to -75 °C. Under a nitrogen atmosphere, a 2.5 M solution of n-butyllithium in hexane (62.6 mL, 156 mmol) was added dropwise over a 15 minute period. After stirring for 1 hour, saturated aqueous sodium bicarbonate was added dropwise to the reaction flask. The dry ice bath was removed and an additional portion of saturated aqueous sodium bicarbonate was added. The mixture was extracted with ethyl acetate (3X) and the combined organic phases dried over anhydrous sodium sulfate and concentrated *in vacuo*. The resulting residue was purified by flash chromatography on silica gel eluting with diethyl ether/hexane (1:6 to 1:5) to give 11.5 g (77% yield) of the title compound (1c) as an oil: $[\alpha]_D^{23}$ -92.1 (c 2.20, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.55-4.36 (m, 1H), 3.53-3.24 (m, 2H), 2.25-1.85 (m, 5H), 1.48 (s, 9H); MS (CI) m/e 196 $(M+H)^+$.

1d. 2-(1-BOC-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine

A 2.34 g (12 mmol) sample of the compound from step 1c above was dissolved in 15 mL of DMF, and $dpppPdCl_2$ (0.6 mmol), CuI (0.74 mmol) and triethylamine (14.25 mmol) were added. The mixture was stirred at room temperature for 1 hour, then 3.14 g (14.4 mmol) of 2-iodo-3-hydroxypyridine (Lancaster Chem. Co.) was added. The reaction mixture was stirred at 60 °C for 16 hours. The solution was cooled, diluted with toluene, and the volatiles were removed under reduced pressure. The residue was dissolved in 1 N HCl, and this solution was extracted with ether. The acidic aqueous layer was adjusted to a

pH 10 with K_2CO_3, and this solution was extracted with methylene chloride. The methylene chloride extract was washed with 20% NaOH, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel, eluting with 100:0 to 95:5 chloroform:methanol to give 980 mg of title compound: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.32 (s, 9H), 1.90-2.20 (m, 4H), 2.95-3.15 (m, 2H), 5.05 (m, 1H), 6.68 (s, 1H), 7.15 (br s, 1H), 7.67 (d, 1H, J=8 Hz), 8.48 (d, 1H, J=3 Hz); MS m/z: 289 $(M+H)^+$.

1e. 2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine dihydrochloride

A 147 mg sample of the compound from step 1b above was dissolved in 4 mL of HCHO and 2 mL of 88% formic acid and heated at reflux for 25 minutes. The solution was cooled, diluted with water, and adjusted to pH 10 with K_2CO_3. The mixture was extracted with methylene chloride, and the extract dried and concentrated. The residue was purified by chromatography on silica gel, eluting with 100:0 to 90:10 chloroform:methanol. The product was dissolved in ethanol, and a solution of HCl in diethyl ether was added dropwise. The resultant white precipitate was then collected by evaporation of solvent and triturated with three portions of diethyl ether to give the title compound (200 mg): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.35-2.37 (m, 2H), 2.58-2.67 (m, 3H), 3.00 (br s, 3H), 3.40 (br s, 1H), 3. 90 (br s, 1H), 7.45 (s, 1H), 7.70 (dd, 1H, J=5, 8.5 Hz), 8.33 (d, 1H, J=8.5 Hz), 8.64 (dd, 1H, J=5, 1 Hz). MS m/z: 203 $(M+H)^+$; Anal. Calcd for $C_{12}H_{14}N_2O$•2.0 HCl•0.2 H_2O•0.1 ethanol: C, 51.99; H, 6.08; N, 9.94. Found: C, 51.59; H, 6.03; N, 9.68.

Example 2

Preparation of 2-(2-(S)-pyrrolidinyl)furo[3,2-b]pyridine dihydrochloride

A 980 mg sample of 2-(1-BOC-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine, from Example 1d above, was dissolved in a solution of TFA in methylene chloride at 0 °C and stirred under N_2 while warming to room temperature. The reaction mixture was diluted with 1 N HCl, and the aqueous layer was separated. The aqueous solution was adjusted to pH 10 with K_2CO_3, and the mixture was extracted with methylene chloride. The solution was dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel and treated with HCl in diethyl ether as described in Example 1e to obtain 280 mg of title compound: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.17-2.52 (m, 3H), 2.65 (m, 1H), 3.57 (dt, 2 H, J=1.5, 7.5 Hz), 5.15 (t, 1H, J=8 Hz), 7.44 (s, 1H), 7.84 (dd, 1H, J=6, 8.5 Hz), 8.5 (dt, 1H, J=1, 8.5 Hz), 8.70 (dd, 1H, J= 1, 6 Hz). MS m/z: 189 $(M+H)^+$, 206 $(M+NH_4)^+$; Anal. Calcd for $C_{11}H_{12}N_2O$•2.0 HCl: C, 50.59; H, 5.40; N, 10.73. Found: C, 50.52; H, 5.26; N, 10.50.

Example 3

Preparation of 2-(2-(R)-pyrrolidinyl)furo[3,2-b]pyridine dihydrochloride

3a. 1-BOC-2-(R)-ethynylpyrrolidine

The title compound was prepared from N-BOC-(R)-proline, first reducing to the prolinol, then according to the procedures of Examples 1a-c above. $[\alpha]_D^{23}$ +113.0 (c 0.94, MeOH).

3b. 2-(1-BOC-2-(R)-pyrrolidinyl)furo[3,2-b]pyridine

A 3.14 g (14.4 mmol) sample of 2-iodo-3-hydroxypyridine (Lancaster Chem. Co.) was dissolved in 5 mL of DMF, and dpppPdCl_2 (0.34 g, 0.50 mmol), CuI (0.371 g, 1.98 mmol) and triethylamine (1.80 mL, 13.2 mmol) were added. The mixture was stirred under N_2 at room temperature for 1 hour, then 2.15 g (11.0 mmol) of the compound from step 3a above, dissolved in 5 mL of DMF, was added carefully. The reaction was stirred at 60 °C for 16 hours, then cooled to room temperature. The reaction mixture was diluted with ether and filtered. The solution was washed with 10% NaOH, 50% brine, dried over $MgSO_4$, and the solvent was removed. The residue was chromatographed on silica gel, eluting with 100:0 to 60:40 hexane:ethyl acetate to give 620 mg of title compound: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.73 (s, 9H), 1.85-2.30 (m, 4H), 3.05-3.22 (m, 2H), 4.42 (m, 1H), 6.78 (s, 1H), 7.16 (dd, 1H), 7.68 (dd, 1H), 8.48 (dd, 1H); MS m/z: 289 $(M+H)^+$.

3c. 2-(2-(R)-pyrrolidinyl)furo[3,2-b]pyridine dihydrochloride

A 614 mg (2.13 mmol) sample of 2-(1-BOC-2-(R)-pyrrolidinyl)furo[3,2-b]pyridine, from step 2b above, was dissolved in 3 mL of methylene chloride, and the solution was cooled to 0 °C. To this solution was added 3 mL of TFA, and the reaction mixture was stirred at 0 °C for 2 hours. The reaction was quenched with saturated aqueous K_2CO_3 solution, and the mixture was extracted with methylene chloride. The organic extract was dried over $MgSO_4$, and the solvent was removed. The residue was purified by chromatography on silica gel and treated with HCl in diethyl ether as described in Example 1e above to obtain the title compound: ^{1}H NMR (D_2O, 300 MHz) δ 2.17-2.69 (m, 4H), 3.52-3.59 (m, 2 H), 5.14 (t, 1H, J=5.5 Hz), 7.42 (t, 1H, J=1 Hz), 7.80 (dd, 1H, J=5.6, 8.5 Hz), 8.5 (dt, 1H, J=1, 8.5 Hz), 8.70 (dd, 1H, J= 1, 5.5 Hz); MS m/z: 189 $(M+H)^+$, 206 $(M+NH_4)^+$; Anal. Calcd for $C_{11}H_{12}N_2O \cdot 2.0\ HCl \cdot 0.5\ H_2O$: C, 48.90; H, 5.60; N, 10.90. Found: C, 48.75: H, 5.74; N, 10.11.

Example 4

Preparation 2-(1-methyl-2-(R)-pyrrolidinyl)furo[3,2-b]pyridine dihydrochloride

A 140 mg sample of the compound from Example 3 above was dissolved in 8 mL of 37% aqueous formaldehyde and 4 mL of 88% formic acid and heated at reflux for 1 hour. The solution was poured into saturated aqueous K_2CO_3 solution, and the mixture was

extracted with methylene chloride. The organic extract was dried, concentrated and purified by chromatography on silica gel, eluting with 100:0 to 95:5 chloroform:methanol. The product was dissolved in ethanol, and a solution of HCl in diethyl ether was added dropwise at ambient temperature. The resultant white precipitate was then collected by evaporation of solvent and triturated with three portions of diethyl ether to give the title compound (60 mg): ^{1}H NMR (D_2O, 300 MHz) δ 2.35 (br, 2H), 2.53-2.70 (m, 3H), 3.00 (br s, 3H), 3.40 (br s, 1H), 3. 90 (br s, 1H), 7.38 (s, 1H), 7.60 (dd, 1H), 8.33 (d, 1H), 8.64 (dd, 1H); MS m/z: 203 $(M+H)^+$, 220 $(M+NH_4)^+$; Anal. Calcd for $C_{12}H_{14}N_2O$•2.0 HCl•1.0 H_2O: C, 49.16; H, 6.19; N, 9.55. Found: C, 49.03; H, 6.08; N, 9.13.

Example 5

Preparation 2-(2-(S)-pyrrolidinyl)-5-methylfuro[3,2-b]pyridine dihydrochloride

5a. 2-(1-BOC-2-(S)-pyrrolidinyl)-5-methylfuro[3,2-b]pyridine

A 3.10 g (13.2 mmol) sample of 2-iodo-2-picoline-5-ol (Aldrich Chem. Co.) was dissolved in 5 mL of DMF, and dpppPdCl_2 (0.38 g, 0.50 mmol), CuI (0.377 g, 1.98 mmol) and triethylamine (1.80 mL, 13.2 mmol) were added. The mixture was stirred under N_2 at room temperature for 1 hour, then 2.15 g (11 mmol) of 1-BOC-2-(S)-ethynylpyrrolidine, from Example 1a above, dissolved in 1 mL of DMF, was added carefully. The reaction was stirred at 60 °C for 16 hours, then cooled to room temperature. The reaction mixture was diluted with 2 N HCl and extracted with ether. The aqueous layer was adjusted to pH 10 with K_2CO_3, then extracted with methylene chloride. The extract was washed with 20% NaOH, brine, dried over $MgSO_4$, and the solvent was removed. The residue was repeatedly dissolved in toluene and distilled to azeotropically remove the DMF. The residue was chromatographed on silica gel, eluting with 100:0 to 50:50 hexane:ethyl acetate to give 521 mg of title compound: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.33 and 1.47 (2 s, 9H), 1.90-2.30 (m, 4H), 2.63 (s, 3H), 3.45-3.65 (m, 2H), 4.95 and 5.10 (2 s, 1H), 5.58 (s, 1H), 7.02 (d, 1H), 7.55 (d, 1H); MS m/z: 303 $(M+H)^+$.

5b. 2-(2-(S)-pyrrolidinyl)-5-methylfuro[3,2-b]pyridine dihydrochloride

To a 530 mg sample of the compound from step 5a above in 4 mL of methylene chloride at 0 °C was added 4 mL of TFA. The reaction mixture was stirred for 16 hours, then diluted with saturated aqueous Na_2CO_3, and extracted with methylene chloride. The organic extract was dried over $MgSO_4$, and the solvent was removed. The residue was chromatographed on silica gel, eluting with 100:0 to 90:10 chloroform:ethanol. The residue was treated with HCl/ether, and the salt was recrystallized from ethanol/ethyl acetate to give 158 mg of title compound: ^{1}H NMR (DMSO, 300 MHz) δ 2.0-2.5 (m, 4H), 2.55 (s, 3H), 3.34 (m, 3H), 4.93 (m, 1H), 7.24 (s, 1H), 7.27 (d, 1H), 7.97 (d, 1H); MS m/z: 203

$(M+H)^+$, 220 $(M+NH_4)^+$; Anal. Calcd for $C_{12}H_{14}N_2O$•2.0 HCl•0.5 H_2O: C. 50.72; H, 6.03; N, 9.86. Found: C, 50.53; H, 6.06; N, 9.62.

Example 6

Preparation of 2-(1-methyl-2-(S)-pyrrolidinyl)-5-methylfuro[3,2-b]pyridine dihydrochloride

A 315 mg (1.04 mmol) sample of 2-(2-(S)-pyrrolidinyl)-5-methylfuro[3,2-b]pyridine dihydrochloride, from Example 5b above, was dissolved in 5 mL of 88% formic acid and 10 mL of 37% aqueous formaldehyde and heated at reflux for 0.5 hours. The reaction mixture was cooled, diluted with 2 N HCl and extracted with ether. The aqueous solution was adjusted to pH 10 with K_2CO_3 and extracted with methylene chloride. The methylene chloride extract was dried over $MgSO_4$, and the solvent was removed. The residue was chromatographed on silica gel, eluting with 100:0 to 95:5 chloroform:ethanol. The residue was converted to the salt by treatment with HCl/ether, and the salt was recrystallized from ethanol/ethyl acetate to give 332 mg of title compound: ^1H NMR (DMSO, 300 MHz) δ 2.13-2.23 (m, 2H), 2.2.35-2.60 (m, 3H), 2.71 (s, 3H), 2.88 (s, 2H), 3.33 (br s, 1H), 3.70 (br s, 1H), 4.88 (m, 1H), 7.54 (d, 1H, J=8.8 Hz), 7.61 (s, 1H), 8.36 (d, 1H, J=8.5 Hz); MS m/z: 217 $(M+H)^+$, 234 $(M+NH_4)^+$; Anal. Calcd for $C_{13}H_{16}N_2O$•2.0 HCl•1.0 H_2O: C, 50.82; H, 6.55; N, 9.12. Found: C, 50.47; H, 6.77; N, 8.92.

Example 7

Preparation of 2-(2-(S)-pyrrolidinyl)-6-chlorofuro[3,2-b]pyridine dihydrochloride

7a. 5-chloro-2-iodo-3-pyridinol

A 20.3 g (0.157 mol) sample of 5-chloro-3-pyridinol (Aldrich Chemical Co.) and 35 g (0.33 mol) of Na_2CO_3 were dissolved in 220 mL of H_2O. To this solution was added 39.9 g of I_2, and the reaction mixture was stirred for 45 minutes. The mixture was then poured slowly into 2 N HCl, and the acidity was adjusted to pH 3. The product was collected by filtration and crystallized from ethanol/ether, affording 23.35 g of title compound: ^1H NMR ($CDCl_3$, 300 MHz) δ 5.45 (s, 1H), 8.0 (d, 1H); MS m/z: 256 $(M+H)^+$, 273 $(M+NH_4)^+$.

7b. 2-(1-BOC-2-(S)-pyrrolidinyl)-6-chlorofuro[3,2-b]pyridine

A 5.63 g (22.0 mmol) sample of 5-chloro-2-iodo-3-pyridinol, from step 7a above, was dissolved in 10 mL of DMF, and dpppPdCl$_2$ (0.38 g, 0.50 mmol), CuI (0.377 g, 1.98 mmol) and triethylamine (1.90 mL, 13.6 mmol) were added. The mixture was stirred under N_2 at room temperature for 1 hour, then 2.15 g (11.0 mmol) of 1-BOC-2-(S)-

ethynylpyrrolidine, from Example 1a above, dissolved in 5 mL of DMF, was added carefully. The reaction was stirred at 60 °C for 16 hours, then cooled to room temperature. The reaction mixture was diluted with ether, then washed with 10% NaOH and brine, then dried over $MgSO_4$. The solvent was removed, and the residue was chromatographed on silica gel, eluting with 100:0 to 60:40 hexane:ethyl acetate to give 2.04 g of title compound: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.3, 1.45 (2 s, 9H), 1.94-2.3 (m, 4H), 3.45-3.65 (m, 2H), 4.97-5.1 (m, 1H), 6.66 (s, 1H), 7.70 (s, 1H), 8.47 (s, 1H); MS m/z: 323 $(M+H)^+$.

7c. 2-(2-(S)-pyrrolidinyl)-6-chlorofuro[3,2-b]pyridine dihydrochloride

To a 2 g sample of the compound from step 7b above in 10 mL of methylene chloride at 0 °C was added 10 mL of TFA, and the reaction mixture was stirred for 1 hour poured into saturated aqueous Na_2CO_3 and extracted with methylene chloride. The organic extract was dried over $MgSO_4$, and the solvent was removed. The residue was chromatographed on silica gel, eluting with 99:1 to 95:5 chloroform:methanol. The product was treated with HCl/ether, and the salt was recrystallized from ethanol/ethyl acetate to give 1.2 g of title compound: ^{1}H NMR (D_2O, 300 MHz) δ 2.18-2.50 (m, 3H), 2.54-2.65 (m, 1H), 3.51-3.36 (m, 2H), 5.06 (t, 1H, J=8 Hz), 7.26 (d, 1H, J=0.7 Hz), 8.24 (dd, 1H, J=0.7, 1.8 Hz), 8.60 (d, 1H, J=1.8 Hz); MS m/z: 223 $(M+H)^+$, 240 $(M+NH_4)^+$; Anal. Calcd for $C_{11}H_{11}N_2OCl{\bullet}2.0$ HCl: C, 44.69; H, 4.43; N, 9.47. Found: C, 44.57; H, 4.31; N, 9.33.

Example 8

Preparation of 2-(1-methyl-2-(S)-pyrrolidinyl)-6-chlorofuro[3,2-b]pyridine dihydrochloride

A 315 mg (1.04 mmol) sample of 2-(2-(S)-pyrrolidinyl)-6-chlorofuro[3,2-b]pyridine dihydrochloride, from Example 7c above, was dissolved in 3 mL of 88% formic acid and 6 mL of 37% aqueous formaldehyde and heated at reflux for 0.5 hour. The reaction mixture was cooled, poured into saturated K_2CO_3, and the mixture was extracted with methylene chloride. The extract was dried over $MgSO_4$, and the solvent was removed. The residue was chromatographed on silica gel, eluting with 100:0 to 95:5 chloroform:methanol. The residue was converted to the salt by treatment with HCl/ether, and the salt was recrystallized from ethanol/ethyl acetate to give 159 mg of title compound: ^{1}H NMR (D_2O, 300 MHz) δ 2.31-2.39 (m, 2H), 2.52-2.70 (m, 3H), 2.96 (br s, 3H), 3.55 (br s, 1H), 3.88 (br s, 1H), 7.33 (s, 1H), 8.13 (dd, 1H), 8.56 (d, 1H); MS m/z: 237 $(M+H)^+$, 254 $(M+NH_4)^+$; Anal. Calcd for $C_{12}H_{13}N_2OCl{\bullet}2HCl$: C, 46.55; H, 4.88; N, 9.05. Found: C, 50.75; H, 5.12; N, 9.69.

Example 9

Preparation of 2-(2-(S)-pyrrolidinyl)furo[2,3-c]pyridine dihydrochloride

9a. 4-iodo-3-methoxymethoxypyridine

The title compound was prepared according to the procedure of Winkle and Ronald, *J. Org. Chem.*, 47:2101-2106 (1982).

9b. 3-hydroxy-4-iodopyridine

A 1.48 g (5.3 mmol) sample of 4-iodo-3-methoxymethoxypyridine, from step 9a above, was suspended in 10 mL of 50% aqueous acetic acid and 4 drops of concentrated H_2SO_4, and the mixture was heated at reflux for 20 minutes. The solution was cooled, adjusted to pH 3 with solid Na_2CO_3, diluted with water, and extracted with ethyl acetate. The organic extract was dried over $MgSO_4$, and the solvent was removed to give 0.86 g of the title compound: MS m/z: 223 $(M+H)^+$, 239 $(M+NH_4)^+$.

9c. 2-(1-BOC-2-(S)-pyrrolidinyl)furo[2,3-c]pyridine

A 829 mg (3.7 mmol) sample of 3-hydroxy-4-iodopyridine, from step 9b above, 130 mg (0.18 mmol) of dpppPdCl2, 170 mg (0.74 mmol) of CuI, and 0.6 mL of triethylamine were combined in 10 mL of DMF at ambient temperature and stirred for 3 hours. To this mixture was added a solution of 1-BOC-2-(S)-ethynylpyrrolidine (1.5 g, 7.7 mmol, from Example 1c above) in 5 mL of DMF, and the reaction mixture was stirred at 60 °C for 16 hours. The reaction mixture was cooled to room temperature and diluted with ether. The ether layer was filtered, washed with 10% NaOH then 50% brine, dried over $MgSO_4$, and concentrated. The residue was purified by chromatography on silica gel, eluting with 100:0 to 50:50 hexane:ethyl acetate to give the title compound.

9d. 2-(2-(S)-pyrrolidinyl)furo[2,3-c]pyridine dihydrochloride

To a 700 mg sample of the compound from step 9c above in 5 mL of methylene chloride at 0 °C was added 5 mL of TFA. The reaction mixture was stirred for 1 hour at 0 °C then poured into saturated Na_2CO_3, and the layers were separated. The aqueous layer was extracted with methylene chloride. The combined organic layers were dried over $MgSO_4$ and concentrated, and the residue was chromatographed on silica gel, eluting with 100:0 to 95:5 chloroform:methanol. The product was converted to the salt by treatment with HCl/ether, which was recrystallized from ethanol/ethyl acetate: ^1H NMR (D_2O, 300 MHz) δ 2.19-2.52 (m, 3H), 2.64 (m, 1H), 3.53-3.58 (m, 2H), 5.13 (t, 1H, J=8 Hz), 7.34 (s, 1H), 8.05 (dd, 1H, J=0.8, 5.8 Hz), 8.49 (d, 1H, J=5.8 Hz), 9.07 (s, 1H); MS m/z: 189 $(M+H)^+$, 206 $(M+NH_4)^+$; Anal. Calcd for $C_{11}H_{12}N_2O{\cdot}2.0\ HCl{\cdot}H_2O$: C, 47.33; H, 5.78; N, 10.03. Found: C, 47.32; H, 5.83; N, 9.90.

Example 10

Preparation of 2-(1-methyl-2-(S)-pyrrolidinyl)furo[2,3-c]pyridine dihydrochloride

A 120 mg sample of the compound from Example 9 above was dissolved in 4 mL of formic acid and 2 mL of formalin, and the reaction mixture was heated at reflux for 30 minutes. The reaction mixture was cooled to ambient temperature and poured into saturated K_2CO_3 solution. The resulting mixture was extracted with methylene chloride, the extract was dried, and the solvent was removed. The residue was chromatographed on silica gel, and the compound was converted to the salt by treatment with HCl/ether: ^1H NMR (D_2O, 300 MHz) δ 2.30-2.40 (m, 3H), 2.50-2.74 (m, 1H), 2.98 (s, 3H), 3.45 (br d, 1H), 3.85 (br s, 1H), 4.97 (t, 1H), 7.47 (s, 1H), 8.08 (d, 1H), 8.51 (d, 1H), 9.10 (s, 1H); MS m/z: 203 $(M+H)^+$; Anal. Calcd for $C_{12}H_{14}N_2O \cdot 2\ HCl \cdot 0.5H_2O$: C, 50.70; H, 6.03; N, 9.86. Found: C, 50.69; H, 6.09; N, 9.61.

Example 11

Preparation of 2-(2-(S)-pyrrolidinyl)-5-chlorofuro[3,2-b]pyridine hydrochloride

11a. 3-acetoxy-6-chloropyridine

To a solution of 5-amino-2-chloropyridine (40.0 g, 0.311 mol) in 180 mL of 3:1 1,2-dimethoxyethane/CH_2Cl_2 at –10 °C was slowly added boron trifluoride diethyl etherate (76.5 mL, 0.662 mol). Then a solution of *tert*-butyl nitrite (44.4 mL, 0.373 mol) in 40 mL of 1,2-dimethoxyethane was slowly added over 15 min such that the reaction temperature remained below –5 °C. The mixture was stirred for 10 min at –10 °C then warmed to 0 °C and stirred for an additional 30 min. Pentane was added and the solid was collected by suction filtration (cold pentane wash) to afford 69.1 g of the tetrafluoroborate diazonium salt. This was dissolved in 350 mL of acetic anhydride, warmed to 75 °C (N_2 evolution) and stirred for 3 h. The volatiles were removed *in vacuo* and the dark residue was diluted with Et_2O and washed with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with Et_2O. The combined ethereal extracts were washed with brine, dried ($MgSO_4$), and concentrated. Purification by chromatography (silica gel; hexane/EtOAc 90:10 to 70:30) afforded the title compound as a white solid (29.4 g, 55%): mp 45 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.35 (s, 3H) 7.35 (d, J=8.5 Hz, 1H), 7.48 (dd, J=2.9, 8.5 Hz, 1H), 8.21 (d, J=2.9 Hz, 1H); MS (CI/NH_3) m/z: 172, 174 $(M+H)^+$; 189, 191 $(M+NH_4)^+$.

11b. 6-chloro-3-hydroxypyridine

5-Acetoxy-2-chloropyridine (11.1 g, 64.7 mmol) was dissolved in MeOH at ambient temperature and solid potassium carbonate (4.47 g, 32.4 mmol) was added. After stirring for 2 h, the volatiles were removed *in vacuo* and the residue was diluted with Et_2O and H_2O. The aqueous phase was neutralized to pH 7 by the addition of 1 *N* aqueous HCl. The layers were separated and the aqueous phase was extracted twice with Et_2O. The combined organic extracts were dried ($MgSO_4$) and concentrated to provide the title

compound as a white solid (8.03 g, 96%): mp 155 °C; ^{1}H NMR (CD$_3$OD, 300 MHz) δ 7.20-7.28 (m, 2H), 7.88 (m, 1H); MS (CI/NH$_3$) m/z: 130,132 (M+H)$^+$; 147,149 (M+NH$_4$)$^+$.

11c. 6-chloro-2-iodo-3-pyridinol

To a solution of 6-chloro-3-pyridinol (5 g, from step 11b) and 8.6 g of Na_2CO_3 in 100 mL of water was added 9.8 g of I_2. The mixture was stirred until the iodine color disappeared. The reaction mixture was then adjusted to pH 5 and extracted with ethyl acetate. The extract was dried over $MgSO_4$, and the solvent was removed. The residue was recrystallized from methanol to afford 5.4 g of the title compound: ^{1}H NMR (CD$_3$OD, 300 MHz) δ 7.09 (d, 1H, J=8.5 Hz), 7.20 (d, 1H, J=8.5 Hz); MS m/z: 256 (M+H)$^+$, 273 (M+NH$_4$)$^+$.

11d. 2-(1-BOC-2-(S)-pyrrolidinyl)-5-chlorofuro[3,2-b]pyridine

A 3.07 g (12.0 mmol) sample of 6-chloro-2-iodo-3-pyridinol, from step 11c above, was dissolved in 10 mL of DMF, and dpppPdCl$_2$ (0.38 g, 0.50 mmol), CuI (0.380 g, 1.98 mmol) and triethylamine (1.7 mL, 12 mmol) were added. The mixture was stirred under N_2 at room temperature for 1 hour, then 1.95 g (10.0 mmol) of 1-BOC-2-(S)-ethynylpyrrolidine, from Example 1a above, dissolved in 5 mL of DMF, was added carefully. The reaction mixture was stirred at 60 °C for 16 hours, cooled to room temperature, diluted with ether, washed with 50% brine and dried over $MgSO_4$, then the solvent was removed. The residue was chromatographed on silica gel, eluting with 100:0 to 50:50 hexane:ethyl acetate to give 1.54 g of title compound: ^{1}H NMR (DMSO, 300 MHz, 130 °C) δ 1.37 (two s, 9H), 1.89-2.07 (m, 3H), 2.37 (m, 1H), 3.40-3.54 (m, 1H), 4.98 (m, 1H), 6.72 (s, 1H), 7.26-7.29 (d, 1H, J=8.6 Hz), 7.93-7.96 (d, 1H, J=8.6 Hz); MS m/z: 323 (M+H)$^+$.

11e. 2-(2-(S)-pyrrolidinyl)-5-chlorofuro[3,2-b]pyridine hydrochloride

A 1.5 g sample of the compound from step 11d above was dissolved in 10 mL of methylene chloride and cooled to 0 °C. The solution was stirred under N_2, 10 mL of TFA was added, and the reaction mixture was stirred for 1 hr. The reaction mixture was poured into saturated K_2CO_3, and the mixture was extracted with methylene chloride. The solution was dried over $MgSO_4$, and the solvent was removed. The residue was chromatographed on silica gel, eluting with 99:1 to 95:5 chloroform:methanol. The residue was converted to the salt by treatment with HCl/ether to give 0.78 g of title compound: ^{1}H NMR (D$_2$O, 300 MHz) δ 2.22-2.65 (m, 4H), 3.52-3.57 (m, 2H), 5.06 (t, 1H, J=8 Hz), 7.15 (d, 1H), 7.48 (d, 1H, J=8.6 Hz), 8.1 (d, 1H, J=8.6 Hz); MS m/z: 223 (M+H)$^+$, 240 (M+NH$_4$)$^+$; Anal. Calcd for $C_{11}H_{11}N_2OCl$•1.0 HCl: C, 50.99; H, 4.67 N, 10.81. Found: C, 51.21; H, 4.79; N, 10.55.

Example 12

Preparation of 2-(1-methyl-2-(S)-pyrrolidinyl)-5-chlorofuro[3,2-b]pyridine hydrochloride

A 660 mg (1.04 mmol) sample of 2-(2-(S)-pyrrolidinyl)-5-chlorofuro[3,2-b]pyridine dihydrochloride, from Example 11e above, was dissolved in 5 mL of 88% formic acid and 10 mL of 37% aqueous formaldehyde and heated at reflux for 1 hour. The reaction mixture was cooled, poured into saturated K_2CO_3, and the mixture was extracted with methylene chloride. The extract was dried over $MgSO_4$, and the solvent was removed. The residue was chromatographed on silica gel, eluting with 100:0 to 95:5 chloroform:methanol. The residue was converted to the salt by treatment with HCl/ether to give 540 mg of title compound: ^{1}H NMR (D_2O, 300 MHz) δ 2.28-2.38 (m, 2H), 2.49-2.72 (m, 2H), 2.92 (br s, 3H), 3.41 (m, 1H), 3.80 (m, 1H), 4.84 (m, 1H), 7.50 (d, 1H, J=8.8 Hz), 8.0-3 (d, 1H, J=8.8 Hz), 8.56 (d, 1H); MS m/z: 237 $(M+H)^+$; Anal. Calcd for $C_{12}H_{13}N_2OCl{\cdot}1.0$ HCl: C, 52.07; H, 5.13; N, 10.12. Found: C, 51.85; H, 5.46; N, 9.78.

Example 13

Preparation of 2-(2-(S)-pyrrolidinyl)-5-chlorofuro[2,3-b]pyridine hydrochloride

13a. 5-chloro-3-iodo-2-pyridinol

A 6.48 g sample of 5-chloro-2-pyridinol (Aldrich) and 10.8 g of Na_2CO_3 were dissolved in 250 mL of water. To this solution was added 12.73 g of I_2, and the mixture was stirred until the iodine color disappeared. The reaction mixture was then adjusted to pH 7 and extracted with ethyl acetate. The extract was dried over $MgSO_4$, and the solvent was removed. The residue was recrystallized from ethanol/water to afford 4 g of the title compound: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.71 (d,1H), 8.18 (d, 1H); MS m/z: 256 $(M+H)^+$, 273 $(M+NH_4)^+$.

13b. 2-(1-BOC-2-(S)-pyrrolidinyl)-5-chlorofuro[2,3-b]pyridine

A 3.07 g (12 mmol) sample of 5-chloro-3-iodo-6-pyridinol, from step 13a above, was dissolved in 10 mL of DMF, and dpppPdCl_2 (0.39 g, 0.5 mmol), CuI (0.38 g, 1.98 mmol) and triethylamine (1.7 mL, 12 mmol) were added. The mixture was stirred under N_2 at room temperature for 1 hour, then 1.95 g (10 mmol) of 1-BOC-2-(S)-ethynylpyrrolidine, from Example 1a above, dissolved in 5 mL of DMF, was added carefully. The reaction mixture was stirred at 60 $^\circ$C for 16 hours, cooled to room temperature, diluted with ether and washed with 50% brine. The organic layer was dried over $MgSO_4$and concentrated. The residue was chromatographed on silica gel, eluting with 100:0 to 50:50 hexane:ethyl acetate to give 1.55 g of title compound: MS m/z: 323 $(M+H)^+$.

13c. 2-(2-(S)-pyrrolidinyl)-5-chlorofuro[2,3-b]pyridine hydrochloride

A 0.56 g sample of the compound from step 13b above was dissolved in 3 mL of methylene chloride and cooled to 0 °C. The solution was stirred under N_2, 3 mL of TFA was added, and the reaction mixture was stirred for 1 hour. The reaction mixture was poured into saturated K_2CO_3, and the mixture was extracted with methylene chloride. The solution was dried over $MgSO_4$, and the solvent was removed. The residue was chromatographed on silica gel, eluting with 99:1 to 95:5 chloroform:methanol. The product was converted to the salt by treatment with HCl/ether to give 0.36 g of title compound: ^1H NMR (D_2O, 300 MHz) δ 2.22-2.60 (m, 4H), 3.50 3.56 (m, 2H), 5.01 (t, 1H, J=8.1 Hz), 7.10 (s, 1H,), 7.82 (d, 1H, J=2.3 Hz), 8.33 (d, 1H, J=2.3 Hz); MS m/z: 223 $(M+H)^+$, 240 $(M+NH_4)^+$; Anal. Calcd for $C_{11}H_{11}N_2OCl{\bullet}1.0$ HCl: C, 50.99; H, 4.67 N, 10.81. Found: C, 51.06; H, 4.64; N, 10.65.

Example 14

Preparation of 2-(1-methyl-2-(S)-pyrrolidinyl)-5-chlorofuro[2,3-b]pyridine dihydrochloride

A 200 mg (0.80 mmol) sample of 2-(2-(S)-pyrrolidinyl)-5-chlorofuro[2.3-b]pyridine dihydrochloride, from Example 13c above, was dissolved in 4 mL of 88% formic acid and 8 mL of 37% aqueous formaldehyde and heated at reflux for 1 hour. The reaction mixture was cooled, poured into saturated K_2CO_3, and the mixture was extracted with methylene chloride. The extract was dried over $MgSO_4$, and the solvent was removed. The residue was chromatographed on silica gel, eluting with 100:0 to 95:5 chloroform:methanol. The product was converted to the salt by treatment with HCl/ether to give 140 mg of title compound: ^1H NMR (D_2O, 300 MHz) δ 2.29-2.38 (m, 2H), 2.49-2.68 (m, 2H), 2.95 (br s, 3H), 3.44 (m, 1H), 3.84 (m, 1H), 4.84 (m, 1H), 7.22 (s, 1H), 8.22 (d, 1H, J=2.3 Hz), 8.36 (d, 1H, J=2.4); MS m/z: 237 $(M+H)^+$, 254 $(M+NH_4)^+$; Anal. Calcd for $C_{12}H_{13}N_2OCl{\bullet}1.0$ HCl•0.3 H_2O: C, 51.74; H, 5.28; N, 9.73. Found: C, 51.74; H, 5.28; N, 10.16.

Example 15

Preparation of 2-(Hexahydro-1H-7a-pyrrolizinyl)furo[3,2-b]pyridine hydrochloride

15a. 1,2,3,5,6,7-Hexahydropyrrolizinium perchlorate

The title compound was prepared using the procedures of Miyano *et al.*, *Synthesis*, **1978**: 701-702, and *J. Heterocyclic Chem.*, 19:1465-1468 (**1982**).

15b. 7a-Ethynyl-hexahydro-1H-pyrrolizine

The compound from step 15a above (1.0 g, 4.8 mmol) was added to a solution of 0.5 M ethynylmagnesium bromide (29 mL, 14.3 mmol) in THF at room temperature. The reaction mixture was stirred for 45 minutes, quenched with 15% NaOH solution, and

washed with brine:water (1:1). The aqueous phase was extracted with CH_2Cl_2, and the organic phases were combined, dried ($MgSO_4$), concentrated and chromatographed (silica gel; $CHCl_3$/MeOH, 90:10) to afford an amber oil (463 mg, 71%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.75-2.06 (m, 6H), 2.14-2.23 (m, 2H), 2.33 (s, 1H), 2.53-2.62 (m, 2H), 3.22-3.28 (m, 2H); MS (CI/NH_3) m/z: 136 $(M + H)^+$.

15c. 2-(Hexahydro-1H-7a-pyrrolizinyl)furo[3,2-b]pyridine

2-Iodo-3-pyridinol (902 mg, 4.1 mmol), copper(I) iodide (116 mg, 0.61 mmol), bis(triphenylphosphine)palladium(II) chloride (119 mg, 0.17 mmol) and triethylamine (570 mL, 4.1 mmol) were combined in DMF (4.5 mL) and stirred for one hour. 7a-Ethynyl-hexahydro-1H-pyrrolizine(460 mg, 3.4 mmol) in DMF (1.2 mL) was added dropwise to the rxn vessel and heated at 60 °C for 18 h. The reaction mixture was allowed to cool to ambient temperature and 2 *N* aqueous HCl was added. The heterogeneous mixture was washed with Et_2O (2X), basified with 15% NaOH solution and extracted with CH_2Cl_2 (2X). The CH_2Cl_2 extracts were combined, dried ($MgSO_4$) concentrated and chromatographed (silica gel; $CHCl_3$/MeOH, 96:4) to afford an amber oil which solidified upon storage in the freezer (405 mg, 52%): mp 39-41 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.86-1.97 (m, 6H), 2.24-2.34 (m, 2H), 2.68-2.76 (m, 2H), 3.21-3.28 (m, 2H), 6.77 (s, 1H), 7.12 (dd, J=8.5, 5 Hz, 1H), 7.65 (d, J=8.5 Hz, 1H), 8.46 (d, J=5 Hz, 1H); MS (CI/NH_3) m/z: 229 $(M + H)^+$.

15d. 2-(Hexahydro-1H-7a-pyrrolizinyl)furo[3,2-b]pyridine hydrochloride

The free base (395 mg, 1.73 mmol), from step 15c above, was dissolved in THF (30 mL) and a saturated solution of HCl in Et_2O was added until precipitation ceased. The solvent was decanted and the remaining light yellow solid triturated with THF (2X). The product was recrystallized from MeOH/Et_2O to afford a light yellow powder, (349 mg, 76%): mp 201-203 °C dec.; ^{1}H NMR (DMSO, 300 MHz) δ 2.09-2.37 (m, 6H), 2.62-2.73 (m, 2H), 3.23-3.40 (m, partially buried within water peak, 2H), 3.57-3.70 (m, 2H), 7.40 (dd, J=8, 5 Hz, 1H), 7.53 (s, 1H), 8.05 (dd, J=8, 1 Hz, 1H), 8.56 (dd, J=5, 1 Hz, 1H), 11.35 (br s, quat.NH); MS (CI/NH_3) m/z: 229 $(M +H)^+$; Anal. Calcd for $C_{14}H_{16}N_2O{\cdot}1.1HCl$: C, 62.81; H, 6.51; N, 10.42. Found: C, 62.65; H, 6.42; N, 10.44.

Example 16

Preparation of 2-(Hexahydro-1H-7a-pyrrolizinyl)-5-methylfuro[3,2-b]pyridine dihydrochloride

16a. 2-(Hexahydro-1H-7a-pyrrolizinyl)-5-methylfuro[3,2-b]pyridine

The acetylene compound 7a-Ethynyl-hexahydro-1H-pyrrolizine (450 mg, 3.33 mmol), 2-iodo-6-methyl-3-pyridinol (939 mg, 4.0 mmol), copper(I) iodide (114 mg, 0.6 mmol), bis(triphenylphosphine)palladium(II) chloride (117 mg, 0.17 mmol) and

triethylamine (560 mL, 4.0 mmol) were combined in a similar fashion as that described for Example 1d. The residue was chromatographed (silica gel; $CHCl_3$/MeOH, 96:4) to afford a yellow solid (403 mg, 50%): ^1H NMR ($CDCl_3$) δ 1.85-1.95 (m, 6H), 2.25-2.30 (m, 2H), 2.62 (s, 3H), 2.67-2.75 (m, 2H), 3.19-3.26 (m, 2H), 6.68 (s, 1H), 6.98 (d, J=8 Hz, 1H), 7.54 (d, J=8 Hz, 1H); MS (CI/NH_3) m/z: 243 $(M + H)^+$.

16b. 2-(Hexahydro-1H-7a-pyrrolizinyl)-5-methylfuro[3,2-b]pyridine dihydrochloride

A sample of the compound from step 16a (395 mg, 1.63 mmol) (395 mg, 1.63 mmol) was dissolved in CH_2Cl_2 (20 mL) and a saturated solution of HCl in Et_2O was added dropwise. The solvent was removed to afford a yellow oil/solid (390 mg, 72%): ^1H NMR (D_2O, 300 MHz) δ 2.30-2.48 (m, 6H), 2.75-2.84 (m, 5H), 3.35-3.45 (m, 2H), 3.77-3.85 (m, 2H), 7.39 (s, 1H), 7.62 (d, J=9 Hz, 1H), 8.31 (d, J=9 Hz, 1H); MS (CI/NH_3) m/z: 243 $(M + H)^+$; Anal. Calcd for $C_{15}H_{18}N_2O$·2.0 HCl•1.0 H_2O: C, 54.06; H, 6.65; N, 8.41. Found: C, 54.00; H, 6.33; N, 8.11.

Example 17

Preparation of 2-(Hexahydro-1H-7a-pyrrolizinyl)furo[2,3-c]pyridine dihydrochloride

17a. 2-(Hexahydro-1H-7a-pyrrolizinyl)furo[2,3-c]pyridine

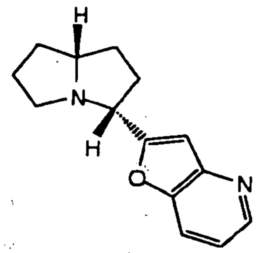
The acetylene compound 7a-ethynyl-hexahydro-1H-pyrrolizine (225 mg, 1.66 mmol), 4-iodo-3-pyridinol (441 mg, 2.0 mmol), copper(I) iodide (60 mg, 0.30 mmol), bis(triphenylphosphine)-palladium(II) chloride (58 mg, 0.08 mmol) and triethylamine (280 mL, 2.0 mmol) were combined in a similar fashion as that described for A-119661.1. The crude was chromatographed (silica gel; $CHCl_3$/MeOH, 98:2 to 95:5) to afford a turbid yellow oil (185 mg, 49%): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.83-1.97 (m, 6H), 2.24-2.31 (m, 2H), 2.67-2.75 (m, 2H), 3.19-3.26 (m, 2H), 6.62 (s, 1H), 7.42 (d, J=5 Hz, 1H), 8.35 (d, J=5 Hz, 1H), 8.77 (s, 1H); MS (CI/NH_3) m/z: 229 $(M + H)^+$.

17b 2-(Hexahydro-1H-7a-pyrrolizinyl)furo[2,3-c]pyridine dihydrochloride

A sample of the compound from step 17a (173 mg, 0.76 mmol) was dissolved in CH_2Cl_2 (10 mL) and a saturated solution of HCl in Et_2O was added until precipitation ceased. The solvent was removed and the product recrystallized from MeOH/Et_2O to afford a light yellow solid (226 mg, 98%): mp 235-238 °C; ^1H NMR (D_2O, 300 MHz) δ 2.30-2.49 (m, 6H), 2.76-2.85 (m, 2H), 3.35-3.45 (m, 2H), 3.77-3.86 (m, 2H), 7.41 (s, 1H), 8.04 (d, J=6 Hz, 1H). 8.49 (d, J=6 Hz, 1H), 9.05 (s, 1H); MS (CI/NH_3) m/z: 229 $(M + H)^+$; Anal. Calcd for $C_{14}H_{16}N_2O$•2.0 HCl•0.8 H_2O: C, 53.28; H, 6.26; N, 8.88. Found: C, 53.61; H, 6.49; N, 8.35.

Example 18

Preparation of *endo*-2-(Hexahydro-1H-3-(R)-pyrrolizidinyl)furo[3,2-b]pyridine dihydrochloride



18a. 3-(N-BOC-2-(R)-pyrrolidinyl)propenal

To a solution of R-prolinal (10.25 g, 51.50 mmol) in 150 mL of anhydrous toluene at room temperature was added (triphenylphosphoranylidene)-acetaldehyde (17.2 g, 56.7 mmol), and the reaction was refluxed for 3 hours under nitrogen. The reaction was concentrated in vacuo. The residue was purified on silica gel, eluting with 1/4 ethyl acetate/hexane. The title compound was obtained as an amber oil in 53% yield (6.13g): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.42 (s (major isomer), 9H), 1.49 (s (minor isomer), 9H), 1.73-1.90 (m, 3H), 2.06-2.24 (m, 1H), 3.37-3.54 (m, 1H), 4.41-4.52 (m (minor isomer), 1H), 4.58-4.68 (m (minor isomer), 1H), 6.11 (qd, 3.0 Hz, 8.0 Hz, 1H), 6.63-6.82 (m, 1H), 9.57 (s (minor isomer), 1H), 9.59 (s (major isomer), 1H); MS(DCI) $(M+H)^+$: 226, $(M+NH_4)^+$: 243.

18b. 3-(N-BOC-2-(R)-pyrrolidinyl)propanal

To a solution of the propenal compound from step 18a (27.20 mmol, 8.02 g) was added 100 mL of ethyl acetate and 0.5 g of 10% Pd/C. The mixture was agitated under 4 atmosphere H_2 for 16 hours. The catalyst removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified on silica gel, eluting with1/4 ethyl acetate/hexane. The title compound was obtained in 97% yield as a yellow oil (5.99g): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.48 (s, 9H), 1.52-1.69 (m, 1H), 1.69-2.01 (m, 5H), 2.39-2.52 (m, 2H). 3.21-3.36 (m, 2H), 3.73-3.94 (m, 1H), 7.27 (s, 1H); MS (DCI) m/z: 228 $(M+H)^+$, 245 $(M+NH_4)^+$.

18c. 5-(N-BOC-2-(R)-pyrrolidinyl)-3-hydroxy-1-pentyne

A solution of the propanal compound from step 18b above (26.40 mmol, 5.99 g) in 100 mL of anhydrous THF under a nitrogen atmosphere was cooled to -78 °C. To this solution was added ethynyl magnesium bromide (0.5 M in THF/79.20 mL), and the reaction was stirred at -78 °C for one hour. The reaction was then warmed to room temperature and stirred for 1.5 hours. The reaction was quenched by pouring it into 200 mL of saturated NH_4Cl. The mixture was extracted with CH_2Cl_2 , dried over Na_2SO_4 and concentrated under vacuum. The residue was purified on silica gel, eluting with1/3 ethyl acetate/hexane. The title compound was obtained in 90% yield as a light yellow oil (5.99 g): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.47 (s, 9H), 1.58-2.00 (m, 8H), 2.41-2.49 (bs, 1H),

3.24-3.37 (m, 3H), 3.66-4.01 (bd, 1H), 4.31-4.51 (m, 1H); MS (DCI) m/z: 254 $(M+H)^+$; 271 $(M+NH_4)^+$.

18d. *endo*-hexahydro-1H-3-(R)-ethynylpyrrolizidine and exo-hexahydro-1H-3-(S)-ethynylpyrrolizidine

To a solution of the alcohol compound from step 18c above (17.30 mmol, 4.38 g) in CH_2Cl_2 (30 mL) at room temperature was added triphenylphosphine dibromide (21.60 mmol, 9.12g), and the reaction was stirred for 16 hours. Next, 5 mL of TFA was added to the reaction, which was stirred for another 4 hours at room temperature. The reaction was then concentrated under vacuum. The residue was purified by chromatography on silica gel, eluting with 10% methanol in methylene chloride containing 1% NH_4OH, to separate the *exo* and *endo* products The combined yield for the reaction was 64%.

endo-(R)- compound: $[\alpha]^{23}_D$ -42.76 (c 0.14, H_2O); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.32-1.48 (m, 2H), 1.69-1.74 (m, 4H), 1.75-2.04 (m, 2H), 2.05-2.71 (m, 1H), 2.75 (d, J=2.0 Hz, 1H), 2.61-2.72 (m, 1H), 3.01-3.13 (m, 1H), 3.32-3.40 (m, 1H), 3.59-3.61 (m, 1H); MS (DCI) m/z: 136$(M+H)^+$, 153 $(M+NH_4)^+$; Anal. Calcd for $C_9H_{13}N$•0.20 H_2O: C,77.87; H, 9.73; N, 10.09. Found: C, 78.15; H, 9.87; N, 10.17.

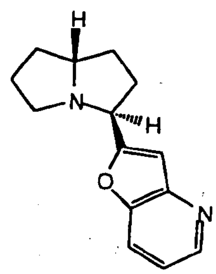
exo-(S)- compound: $[\alpha]^{23}_D$ +51.14 (c 0.37, H_2O); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.33-1.50 (m, 1H), 1.54-1.70 (m, 1H), 1.87-1.89 (m, 1H), 1.89-2.19 (m, 5H), 2.22 (d, J=2.0 Hz, 1H), 2.83-2.96 (m, 1H), 3.01-3.13 (m, 1H), 3.47-3.59 (m, 1H), 3.84-3.92 (m, 1H); MS (DCI) m/z: 136 $(M+H)^+$, 153 $(M+NH_4)^+$; Anal. Calcd for $C_9H_{13}N$•0.10 H_2O: C,78.89; H, 9.71; N, 10.22. Found: C, 78.88; H, 9.59; N, 10.05.

18e. *endo*-2-(hexahydro-1H-3-(R)-pyrrolizidinyl)furo[3,2-b]pyridine dihydrochloride

To DMF (5.0 mL) in a flask purged with nitrogen was added 2-iodo-3-hydroxypyridine (1.20 mmol, 0.2652 g), bis(triphenylphosphine)-palladium(II) chloride (0.05 mmol, 35 mg), copper(I)Iodide (0.20 mmol, 38.1 mg), and triethylamine (1.2 mmol, 0.1214 g), and the reaction was stirred for one hour at room temperature. The endo-(R)-acetylene compound from step 18d above was then added (1.0 mmol, 0.134 g) in 5.0 mL of DMF, and the reaction was heated at 60 °C for 16 hours. The reaction was cooled and poured into 2 N HCl (100 mL), and the mixture was extracted with CH_2Cl_2 (2x75 mL). The aqueous layer was basified with solid K_2CO_3 and extracted with CH_2Cl_2, and the extract was dried over $MgSO_4$ and concentrated under vacuum. The residue was purified on silica gel, eluting with 10% MeOH in CH_2Cl_2. The title compound was obtained by treating the base with a saturated solution of HCl/EtOH at 0 °C: $[\alpha]_D^{23}$ +26.21 (c 0.12, methanol); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.96-2.13 (m, 2H), 2.15-2.40 (m, 3H), 2.51-2.78 (m, 3H), 3.57-3.69 (m, 2H), 4.45-4.57 (m, 1H), 4.96-5.08 (m, 1H), 7.65 (bs, 1H), 7.95-8.07 (m, 1H), 8.28-8.37 (m, 1H), 8.51-8.71 (d, J=10,0 Hz, 1H); MS (DCI) m/z: 229 $(M+H)^+$, 246 $(M+NH_4)^+$; Anal. Calcd for $C_{14}H_{16}N_2O$•2.2 HCl•1.1 H_2O: C, 51.21; H, 6.26; N, 8.53. Found: C, 51.27; H, 6.05; N, 8.31.

Example 19

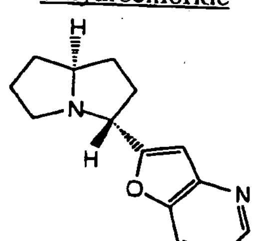
Preparation of exo-2-(Hexahydro-1H-3-(S)-pyrrolizidinyl)furo[3,2-b]pyridine dihydrochloride



Following the procedures of Example 18e above, substituting the *exo*-hexahydro-1H-3-(S)-ethynylpyrrolizidine compound from Example 18d above for the endo-(R) compound of step 18e, the title compound was prepared. $[\alpha]_D^{23}$ -21.28 (c 0.10, methanol); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.78-2.00 (m, 2H), 2.06-2.24 (m, 2H), 2.36-5.52 (m, 2H), 2.53-2.78 (m, 2H), 2.90-3.03 (m, 1H), 3.21-3.30 (m, 1H), 4.42-4.53 (m, 1H), 5.17-5.29 (m, 1H), 7.61 (s, 1H), 7.89 (dd, J=9.0 Hz, J=11.0 Hz, 1H), 8.62 (d, J=12.0 Hz, 1H), 8.27-8.38 (m, 1H); MS (DCI) m/z: 229 $(M+H)^+$, 246 $(M+NH_4)^+$; Anal. Calcd for $C_{14}H_{16}N_2O{\bullet}2.40\ HCl{\bullet}0.50\ H_2O$: C, 51.87; H, 6.02; N, 8.49. Found: C, 51.87; H, 5.71; N, 8.49.

Example 20

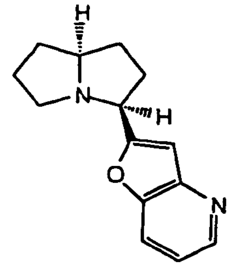
Preparation of exo-2-(Hexahydro-1H-3-(R)-pyrrolizidinyl)furo[3,2-b]pyridine dihydrochloride



Following the procedures of Example 18, substituting (S)-prolinal for the (R)-starting material of step 18a therein, and carrying the reactions forward as in steps 18b, c, and d, then separating the exo-(R)- and endo-(S)-isomers and carrying the exo-(R)-compound forward according to the procedures of step 18e, the title compound was prepared. The MS and NMR data were similar to the compound of Example 18e. $[\alpha]_D^{23}$ -24.68 (c 0.16, methanol).

Example 21

Preparation of *endo*-2-(Hexahydro-1H-3-(S)-pyrrolizidinyl)furo[3,2-b]pyridine dihydrochloride



Following the procedures of Example 18e above, substituting the endo-hexahydro-1H-3-(S)-ethynylpyrrolizidine compound from Example 20d above for the endo-(R) compound of step 18e, the title compound was prepared. The MS and NMR data were similar to the compound of Example 18e. $[\alpha]_D^{23}$ +31.01 (c 0.21, methanol).

Example 22

Preparation of 1-Pyrrolidinylmethyl-(2-furo[3,2-b]pyridine)

To DMF (20.0 mL) in a flask purged with nitrogen was added a solution of 2-iodo-3-hydroxypyridine (18.60 mmol, 4.11 g) , bis(triphenylphosphine)-palladium(II) chloride (0.80 mmol, 0.544 g), copper(I) iodide (3.10 mmol, 0.590 g), and triethylamine (18.60 mmol, 2.59 g) in DMF (20 mL), and the mixture was stirred for one hour at room temperature. To this solution was then added N-(3-propynylpyrrolidine (15.50 mmol, 1.68 g, prepared according to Biehl and DiPierro, *J. Am. Chem. Soc.*, 80, 4609-4614, **1958**), in DMF (10.0 mL), and the mixture was heated at 60 °C for 16 hours. The mixture was cooled, poured into 4 N HCl (100 mL) and extracted with methylene chloride. The aqueous phase was then basified with 15% NaOH and extracted with methylene chloride. The extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by chromatography, eluting with 10% methanol/CH_2Cl_2 to give the title compound in 72% yield: ^1H NMR (300 MHz): δ 2.25 (bs, 4H), 3.64 (bs, 4H), 4.88 (s, 2H), 7.57 (s, 1H), 7.90 (dd, J=5.37, 13.67 Hz, 1H), 8.56 (d, J=8.30 Hz, 1H), 8.80 (d, J=5.86 Hz, 1H). MS (DCI): $(M+H)^+$, 203; $(m+NH_4)^+$, 220. Anal. Calcd for $C_{14}H_{16}Cl_2N_2O$•2.0 HCl•0.1 H_2O: C, 52.03; H, 5.89; N,10.11. Found C, 51.72; H, 6.12; N, 10.05

Example 23

Preparation of 5-Chloro-2-(hexahydro-1H-7a-pyrrolizinyl)furo[3,2-b]pyridine hydrochloride

23a. 5-Chloro-2-(hexahydro-1H-7a-pyrrolizinyl)furo[3,2-b]pyridine

N-(3-propynylpyrrolidine (225 mg, 1.66 mol, prepared according to Biehl and DiPierro, *J. Am. Chem. Soc.*, 80, 4609-4614, **1958**), 6-chloro-2-iodo-3-pyridinol (509 mg, 2.0 mmol), copper(I) iodide (60 mg, 0.30 mmol), bis(triphenylphosphine)palladium(II) chloride (58 mg, 0.08 mmol) and triethylamine (0.280 mL, 2.0 mmol) were combined in a similar fashion as that described for Example 15. The crude product was chromatographed (silica gel; $CHCl_3$/MeOH, 97.5:2.5) to afford a waxy tan solid (335 mg, 77%): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.88-1.97 (m, 6H), 2.21-2.33 (m, 2H), 2.67-2.79 (m, 2H), 3.19-3.26 (m, 2H), 6.70 (s, 1H), 7.14 (d, J=8.5 Hz, 1H), 7.61 (d, J=8.5 Hz, 1H); MS (CI/NH_3) m/z: 263 $(M + H)^+$.

23b. 5-Chloro-2-(hexahydro-1H-7a-pyrrolizinyl)furo[3,2-b]pyridine hydrochloride

The compound from step 23a (325 mg, 1.24 mmol) was dissolved in CH_2Cl_2 (10 mL) and a saturated solution of HCl in Et_2O was added dropwise. The solvent was removed and the product recrystallized from MeOH/Et_2O to afford a white solid (223 mg, 58%): mp 233-235 °C; ^1H NMR (D_2O, 300 MHz) δ 2.32-2.45 (m, 6H), 2.75-2.83 (m, 2H), 3.31-3.43 (m, 2H), 3.75-3.83 (m, 2H), 7.23 (s, 1H), 7.49 (d, J=9 Hz, 1H), 8.01 (d, J=9 Hz, 1H); MS (CI/NH_3) m/z: 263 $(M + H)^+$; Anal. Calcd for $C_{14}H_{15}ClN_2O \cdot 1.2$ HCl: C, 54.86; H, 5.33; N, 9.14. Found: C, 54.61; H, 5.36; N, 8.98.

Example 24

Preparation of 2-(Hexahydro-1H-7a-pyrrolizinyl)thieno[3,2-b]pyridine hydrochloride

24a. 2-(Hexahydro-1H-7a-pyrrolizinyl)thieno[3,2-b]pyridine

Thieno[3,2-b]pyridine (200 mg, 1.48 mmol) prepared according to S. Gronowitz *et al.*, *Acta Chemica Scandinavica B* **1975**, *29*: 233-238 was dissolved in THF (6 mL) and nBuLi (0.6 mL, 1.5 mmol) 2.5 M in hexanes was added at 0 °C. After 10 minutes of stirring, 1,2,3,5,6,7-hexahydro-pyrrolizinylium perchlorate (155 mg, 0.74 mmol) was added en bulk. The slurry was allowed to gradually warm to ambient temperature and stir an additional two hours. The reaction mixture was partitioned between 2 *N* aqueous HCl and Et_2O. The phases were separated and the aqueous phase basified with 15% NaOH solution and then extracted with CH_2Cl_2 (3X). The organic phases were combined, dried ($MgSO_4$) and concentrated. The residue was chromatographed (silica gel; $CHCl_3$/MeOH, 100:0 to 99:1) to afford a yellow solid (115 mg, 63%): mp 94-96 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.80-1.96 (m, 4H), 2.00-2.09 (m, 2H), 2.18-2.26 (m, 2H), 2.64-2.72 (m, 2H), 3.23-

3.30 (m, 2H), 7.13 (dd, J=8, 4 Hz, 1H), 7.23 (s, 1H), 8.05 (dd, J=8, 1.5 Hz, 1H), 8.58 (dd, J=4, 1.5 Hz, 1H); MS (CI/NH_3) m/z: 245 $(M + H)^+$.

24b. 2-(Hexahydro-1H-7a-pyrrolizinyl)thieno[3,2-b]pyridine hydrochloride

The compound from step 24a (104 mg, 0.43 mmol) was dissolved in CH_2Cl_2 (3 mL) and a saturated solution of HCl in Et_2O was added dropwise. The solvent was removed and the product dried *in vacuo* to afford a hygroscopic yellow solid (124 mg, 93%): ^1H NMR (D_2O, 300 MHz) δ 2.30-2.48 (m, 4H), 2.51-2.60 (m, 2H), 2.77-2.86 (m, 2H), 3.36-3.44 (m, 2H), 3.79-3.88 (m, 2H), 7.67 (dd, J=8, 5 Hz, 1H), 7.84 (s, 1H), 8.70 (dd, J=8, 1 Hz, 1H), 8.75 (dd, J=5, 1 Hz, 1H); MS (CI/NH_3) m/z: 245 $(M + H)^+$; Anal. Calcd for $C_{14}H_{16}N_2S{\bullet}1.8\ HCl$: C, 54.25; H, 5.79; N, 9.04. Found: C, 54.25; H, 5.81; N, 8.75.

Example 25

Preparation of 5,6-Dichloro-2-(2-(S)-pyrrolidinyl)furo[3,2-b]pyridine hydrochloride

5,6-dichloro-2-(1-t-butyloxycarbonyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine

5,6-Dichloro-2-iodo-3-pyridinol (750 mg, 2.6 mmol), copper(I) iodide (89 mg, 0.47 mmol), bis(triphenylphosphine)palladium(II) chloride (91 mg, 0.13 mmol) and triethylamine (433 mL, 3.1 mmol) were combined in DMF (3.0 mL) and allowed to stir for 1 hour. 1-t-Butyloxycarbonyl-2-(S)-ethynylpyrrolidine (610 mg, 3.1 mmol) in DMF (1 mL) was added and the reaction mixture heated to 60°C for 16 hours. After cooling to ambient temperature, the reaction mixture was poured over Et_2O/saturated K_2CO_3 solution and the phases separated. The organic phase was washed with brine:water (1:1) (4X), dried ($MgSO_4$), concentrated and chromatographed (silica gel; EtOAc/hexane, 1:6) to afford an amber oil (408 mg, 44%): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.32 and 1.45 (two br s, 9H), 1.95-2.40 (m, 4H), 3.45-3.74 (m, 2H), 5.02 (m, 1H), 6.62 (s, 1H), 7.81 (s, 1H); MS (CI/NH_3) m/z: 357 $(M + H)^+$.

25b. 5,6-Dichloro-2-(2-(S)-pyrrolidinyl)furo[3,2-b]pyridine

The compound from step 25a (400 mg, 1.12 mmol) was dissolved in CH_2Cl_2 (3 mL) and TFA (3 mL) added at ambient temperature. After stirring for 1 hour, the solvent was removed and the residue redissolved in CH_2Cl_2 and washed with saturated K_2CO_3 solution, dried ($MgSO_4$) and concentrated. The crude product was chromatographed (silica gel; $CHCl_3$/MeOH, 98:2) to afford a solid (206 mg, 71%): mp 98-100 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.81-2.05 (m, 3H), 2.22 (m, 1H), 3.04-3.20 (m, 2H), 4.40 (m, 1H), 6.70 (s, 1H), 7.80 (s, 1H); MS (CI/NH_3) m/z: 257 $(M + H)^+$.

25c. 5,6-Dichloro-2-(2-(S)-pyrrolidinyl)furo[3,2-b]pyridine hydrochloride

The compound from step 22b above (54 mg, 0.21 mmol) was slurried in Et_2O and a saturated solution of HCl in Et_2O was added dropwise. The solvent was removed and the

product recrystallized from MeOH/Et_2O to afford a white solid (48 mg, 78%): $[\alpha]_D^{20}$ +5.3 (c 0.51, MeOH); ^{1}H NMR (D_2O, 300 MHz) δ 2.18-2.65 (m, 4H), 3.51-3.56 (m, 2H), 5.05 (dd, J=8, 8 Hz, 1H), 7.16 (d, J=1 Hz, 1H), 8.24 (d, J=1 Hz, 1H); MS (CI/NH_3) m/z: 257 $(M + H)^+$; Anal. Calcd for $C_{11}H_{10}Cl_2N_2O$•HCl: C, 45.00; H, 3.78; N, 9.54. Found: C, 45.08; H, 3.59; N, 9.40.

Example 26

Preparation of 5,6-Dichloro-2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine hydrochloride

26a. 5,6-Dichloro-2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine

The amine from Example 25b (145 mg, 0.57 mmol) was dissolved in an aqueous solution of 37% formaldehyde (excess) and 88% formic acid (excess). The aqueous mixture was heated to 90 °C for 1.5 hours and then allowed to cool to ambient temperature. The reaction mixture was washed with Et_2O, basified with 15% NaOH solution and extracted with CH_2Cl_2 (3X). The organic phases were combined, dried ($MgSO_4$), concentrated and chromatographed (silica gel; $CHCl_3$/MeOH, 98:2) to afford a white solid (97 mg, 62%): mp 58-60 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.89 (m, 1H), 2.00-2.17 (m, 2H), 2.24 (m, 1H), 2.33 (s, 3H), 2.39 (m, 1H), 3.26 (m, 1H), 3.43 (m, 1H), 6.74 (s, 1H), 7.83 (s, 1H); MS (CI/NH_3) m/z: 271 $(M + H)^+$.

26b. 5,6-Dichloro-2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine hydrochloride

The compound from step 26b (92 mg, 0.34 mmol) was slurried in Et_2O and a saturated solution of HCl in Et_2O was added dropwise. The solvent was removed and the product recrystallized from MeOH/Et_2O to afford a white solid (70 mg, 67%): mp 249-251 °C; ^{1}H NMR (D_2O, 300 MHz) δ 2.27-2.37 (m, 2H), 2.47-2.71 (m, 2H), 2.93 (s, 3H), 3.38 (m, 1H), 3.74-3.83 (m, 1H), 4.78-4.85 (m, partially buried under H_2O peak, 1H), 7.27 (s, 1H), 8.26 (s, 1H); MS (CI/NH_3) m/z: 271 $(M + H)^+$; Anal. Calcd for $C_{12}H_{12}Cl_2N_2O$.1.2 HCl: C, 45.77; H, 4.23; N, 8.82; Found: C, 45.61; H, 4.36; N, 8.90.

Example 27

Preparation of 2-(Hexahydro-1H-7a-pyrrolizinyl)-4-methylthieno[3,2-b]pyridine dihydrochloride

27a. 2-(Hexahydro-1H-7a-pyrrolizinyl)-4-methylthieno[3,2-b]pyridine

5-Methylthieno[3,2-b]pyridine (285 mg, 1.91 mmol, prepared according to Gronowitz *et al., Acta Chemica Scandinavica B*, 29:233-238 (**1975**)) and diisopropylamine (270 mL, 1.91 mmol) were combined in THF (8 mL). After 20 minutes of stirring,

1,2,3,5,6,7-hexahydro-pyrrolizinylium perchlorate (200 mg, 0.95 mmol) was added en bulk. The reaction was allowed to warm to ambient temperature and 2 *N* aqueous HCl added. The reaction mixture was washed with Et_2O and the aqueous phase basified with 15% NaOH solution and extracted with CH_2Cl_2 (3X). The organic phases were combined, dried ($MgSO_4$), concentrated and chromatographed (silica gel; $CHCl_3$/MeOH, 99:1) to afford a solid (79 mg, 32%): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.80-1.94 (m, 4H), 1.98-2.07 (m, 2H), 2.16-2.24 (m, 2H), 2.64 (s, 3H), 2.64-2.71 (m, 2H), 3.22-3.28 (m, 2H), 7.02 (d, J=8 Hz, 1H), 7.16 (s, 1H), 7.92 (d, J=8 Hz, 1H); MS (CI/NH_3) m/z: 259 $(M + H)^+$.

27b. 2-(Hexahydro-1H-7a-pyrrolizinyl)-4-methylthieno[3,2-b]pyridine dihydrochloride

The compound from step 27a (73 mg, 0.28 mmol) was dissolved in CH_2Cl_2 and treated with a saturated solution of HCl in Et_2O to afford a hygroscopic foam-like solid (100 mg, quantitative): mp 233-235 °C; ^1H NMR (D_2O, 300 MHz) δ 2.28-2.49 (m, 4H), 2.55-2.64 (m, 2H), 2.77-2.86 (m, 2H), 2.89 (s, 3H), 3.38-3.47 (m, 2H), 3.82-3.90 (m, 2H), 7.78 (d, J=8.5 Hz, 1H), 7.90 (s, 1H), 8.90 (d, J=8.5 Hz, 1H); MS (CI/NH_3) m/z: 259 $(M + H)^+$; Anal. Calcd for $C_{15}H_{18}N_2S$•1.3 HCl•0.9 H_2O: C, 50.26; H, 6.21; N, 7.81. Found: C, 50.68; H, 6.40; N, 7.41.

Example 28

Preparation of 2-(2-(S)-pyrrolidinyl)-5-bromofuro[3,2-b]pyridine hydrochloride

28a. 3-amino-6-bromopyridine

A mixture of 2-bromo-5-nitropyridine (30.75 g, 151.5 mmol), water (250 mL), and acetic acid (110 mL) was heated to 45 °C. Iron powder (24.5 g, 439 mmol) was added at a rate which kept the temperature below 53 °C, then the mixture was stirred at 48 °C ± 5 °C. The mixture was cooled to room temperature and filtered through diatomaceous earth. The filter cake was washed with ethyl acetate, and the aqueous mixture was extracted with ethyl acetate. The combined organic fractions were washed with saturated Na_2CO_3 and brine, dried over $MgSO_4$, and the solvent was removed *in vacuo*. The residue was chromatographed on silica gel, eluting with 100:0 to 50:50 hexane:ethyl acetate to give 20.4 g of the title compound: ^1H NMR ($CDCl_3$ 300 MHz) δ 6.86-6.90 (dd, 1H, J=8.5, 2.4 Hz) 7.21-7.23 (d, 1H, J=8.2 Hz) 7.85-7.86 (d, 1H, J=3 Hz); MS m/z: 173 $(M+H)^+$, 190 $(M+NH_4)^+$.

28b. 5-acetoxy-2-bromopyridine

To 25.6 mL of boron trifluoride etherate (208 mmol, Aldrich) cooled to -15 °C under N_2 was added 18 g (104 mmol) of 5-amino-2-bromopyridine (from step 28a above) dissolved in 35 mL of DME. Then *tert*-butyl nitrite (14.7 mL, 125 mmol, Aldrich) was added at a rate which kept the temperature below 0 °C. DME (65 mL) and methylene

chloride (60 mL) were then added. After 10 minutes at -10 °C the mixture was warmed to 5 °C and stirred for 30 min. Pentane (400 mL) was then added to the reaction mixture, the solid was collected by suction filtration, washed with cold ether, air dried, and dissolved in 125 mL acetic anhydride. The resulting solution was heated to 100 °C ± 5 °C for 1 hour. The solvent was removed *in vacuo*, and the residue was suspended in saturated aqueous Na_2CO_3, and extracted with ethyl ether. The ether solution was dried over $MgSO_4$, the solvent was removed *in vacuo*, and the residue was chromatographed on silica gel, eluting with 100:0 to 60:40 hexane:ethyl acetate to give 13.6 g of the title compound: ^1H NMR ($CDCl_3$ 300 MHz) δ 2.35 (s, 3H) 7.36-7.39 (dd, 1H), 7.49-7.52 (d, 1H), 8.19-8.21 (d, 1H) MS m/z: 216 $(M+H)^+$, 233 $(M+NH_4)^+$.

28c. 2-bromo-5-hydroxypyridine

5-Acetoxy-2-bromopyridine (12.8 g, 60 mmol, from step 28b) was dissolved in 15% aqueous NaOH (50 mL) at 0 °C, and the solution was warmed to room temperature and stirred for 60 minutes. After complete consumption of the starting material the solution was neutralized by addition of 1 N HCl. The aqueous mixture was extracted with ethyl acetate (3 X 200 mL). The organic extracts were washed with brine (4 X 50 mL), water (2 X 50 mL), dried (MgS04), and the solvent was evaporated to yield 9.8 g of the title compound: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.12-7.16 (dd, 1H, J=3.2 Hz),7.36-7.39 (d, 1H, J=8.5Hz), 8.04-8.05 (d, 1H, J=2.4 Hz) MS m/z: 174 $(M+H)^+$.

28d. 6-bromo-2-iodo-3-pyridinol

A 4.125 g sample of 6-bromo-3-pyridinol (from step 28c) and 5.28 g of Na_2CO_3 were dissolved in 75 mL of water. To this solution was added 6.02 g of I_2, and the mixture was stirred until the dark iodine color disappeared. The reaction mixture was then adjusted to pH 5, and extracted with ethyl acetate. The extract was dried over $MgSO_4$, and the solvent was removed. The residue was chromatographed on silica gel, eluting with 97:3 $CHCl_3$:MeOH to give 4.3 g of the title compound: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.08-7.11(d, 1H, J=8.51Hz), 7.29-7.32 (d, 1H, J=8.5 Hz); MS m/z: 300 $(M+H)^+$, 317 $(M+NH_4)^+$.

28e 2-(1-BOC-2-(S)-pyrrolidinyl)-5-bromofuro[3,2-b]pyridine

A 1.84 g (6.10 mmol) sample of 6-bromo-2-iodo-3-pyridinol, from step 28d above, was dissolved in 10 mL of DMF, and dpppPdCl_2 (0.30 g, 0.4 mmol), CuI (0.3 g, 1.6 mmol) and triethylamine (1.2 mL, 8.5 mmol) were added. The mixture was stirred under N_2 at room temperature for 1 hour, then 1.3 g (6.7 mmol) of 1-BOC-2-(S)-ethynylpyrrolidine, from Example 1a above, dissolved in 5 mL of DMF, was added carefully. The reaction was stirred at 80 °C for 16 hours, then cooled to room temperature. The reaction mixture was diluted with ether, then washed with 50% brine, and the extract was dried over $MgSO_4$. The solvent was removed, and the residue was chromatographed on silica gel, eluting with 100:0 to 60:40 hexane:ethyl acetate to give 1.4 g of title

compound: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.31(s, 9H), 1.89-2.06 (m, 3H), 2.27-2.34 (m, 1H), 3.43-3.5 (m, 2H), 4.96-5.0 (m, 1H), 6.72 (s, 1H), 7.38-7.41 (d, 1H, J =8.6 Hz), 7.83-7.86 (d, 1H, J =8.6 Hz); MS m/z: 367 $(M+H)^+$.

28f. 2-(2-(S)-pyrrolidinyl)-5-bromofuro[3,2-b]pyridine hydrochloride

To a solution of the product from step 28d above (1.2 g) in 10 mL of methylene chloride at 0 °C was added 10 mL of TFA. The reaction mixture was stirred for 1 hour, the mixture was poured into saturated K_2CO_3, and the aqueous solution was extracted with methylene chloride. The organic extract was dried over $MgSO_4$, and the solvent was removed. The residue was chromatographed on silica gel, eluting with 99:1 to 95:5 chloroform:methanol. The residue was converted to the salt by treatment with HCl/ether to give 0.6 g of the title compound: ^1H NMR (D_2O, 300 MHz) δ 2.30-2.63 (m, 4H), 3.51-3.56 (m, 2H), 5.02-5.07 (t, 1H, J=7.7 Hz), 7.15 (s, 1H,), 7.61-7.64 (d, 1H, J=8.8 Hz), 7.91-7.95 (d, 1H, J=8.8 Hz).; MS m/z: 267 $(M+H)^+$, 282 $(M+NH_4)^+$; Anal. Calcd for $C_{11}H_{11}N_2OCl$•1.0 HCl: C, 43.52; H, 3.98 N, 9.23. Found: C, 43.53; H, 4.08; N, 9.13.

28g 2-(1-methyl-2-(S)-pyrrolidinyl)-5-Br-furo[3,2-b]pyridine dihydrochloride

A 300 mg sample of the compound from step 28f above was dissolved in an aqueous solution of 37 % formaldehyde (4 mL) and 88 % formic acid (2 mL) and heated at reflux for 1 hour. The solution was cooled, diluted with water, and adjusted to pH 10 with K_2CO_3. The mixture was extracted with methylene chloride, and the extract dried and concentrated. The residue was purified by chromatography on silica gel, eluting with 100:0 to 97:3 chloroform:methanol. The product was dissolved in ethanol at ambient temperature and a solution of hydrochloric acid in diethyl ether was added dropwise. The resultant white precipitate was then collected by evaporation of solvent and triturated with three portions of diethyl ether to give the title compound (163 mg, 43 %): ^1H NMR (D_2O, 300 MHz) δ 2.28-2.39 (m 2H), 2.49-2.72 (m, 2H), 2.95 (s, 3H), 3.38 (m, 1H), 3.80 (m, 1H), 4.85 (m, 1H), 7.27 (s, 1H), 7.96 (d, 1H, J=1.02 Hz), 7.96 (d, 1H, J=1.02 Hz); MS m/z; 281 $(M+H)^+$; Anal. Calcd for $C_{12}H_{13}N_2OBr$•1.0 HCl: C, 45.38; H, 4.44 N, 8.82. Found: C, 45.11; H, 4.17; N, 8.52.

Example 29

Preparation of 2-(2-(R)-pyrrolidinyl)-5-methylfuro[3,2-b]pyridine hydrochloride

The title compound was prepared from 1-Boc-2(R)-ethynylpyrrolidine according to the procedures of Example 5 above: $[\alpha]_D^{23}$ = +16.5° (c 1.0, methanol); Anal. Calcd for $C_{12}H_{14}N_2O$•2.0 HCl•0.2 H_2O•0.2 ethanol: C, 51.39; H, 6.19; N, 9.67. Found: C, 51.63; H, 6.49; N, 9.33.

Example 30

Preparation of 2-(1-methyl-2-(R)-pyrrolidinyl)-5-methylfuro[3,2-b]pyridine dihydrochloride

The title compound was prepared from 1-Boc-2(R)-ethynylpyrrolidine according to the procedures of Example 6 above: Anal. Calcd for $C_{13}H_{16}N_2O{\bullet}2.0\ HCl{\bullet}0.4\ H_2O$: C, 52.68; H, 6.39; N, 9.145. Found: C, 52.70; H, 6.27; N, 9.32.

Example 31

Preparation of 2-(2-(R)-pyrrolidinyl)-6-chlorofuro[3,2-b]pyridine hydrochloride

The title compound was prepared from 1-Boc-2(R)-ethynylpyrrolidine according to the procedures of Example 13 above: Anal. Calcd for $C_{11}H_{11}N_2OCl{\bullet}1.0\ HCl$: C, 50.99; H, 4.67 N, 10.81. Found: C, 50.91; H, 4.75; N, 10.86.

Example 32

Preparation of 2-(1-methyl-2-(R)-pyrrolidinyl)-5-chlorofuro[3,2-b]pyridine hydrochloride

The title compound was prepared from 1-Boc-2(R)-ethynylpyrrolidine according to the procedures of Example 12 above: Anal. Calcd for $C_{12}H_{13}N_2OCl{\bullet}1.8\ HCl$: C, 47.67; H, 4.93; N, 9.27. Found: C, 47.49; H, 5.08; N, 8.97.

Example 33

Preparation of 2-(2-(R)-pyrrolidinyl)-5-bromofuro[3,2-b]pyridine hydrochloride

The title compound was prepared from 1-Boc-2(R)-ethynylpyrrolidine according to the procedures of Examples 28 above: Anal. Calcd for $C_{11}H_{11}N_2OCl{\bullet}1.0\ HCl$: C, 43.52; H, 3.98 N, 9.23. Found: C, 43.40; H, 4.05; N, 8.98

Example 34

Preparation of 2-(2-(R)-pyrrolidinyl)furo[2,3-c]pyridine dihydrochloride

The title compound was prepared from 1-Boc-2(R)-ethynylpyrrolidine according to the procedures of Example 9 above: Anal. Calcd for $C_{11}H_{12}N_2O{\bullet}2\ HCl$: C, 50.58; H, 5.40; N, 10.73. Found: C, 50.38; H, 5.37; N, 10.51.

Example 35

Preparation of 2-(2-(R)-pyrrolidinyl)-5-chlorofuro[3,2-b]pyridine hydrochloride

The title compound was prepared from 1-Boc-2(R)-ethynylpyrrolidine according to the procedures of Example 11 above: Anal. Calcd for $C_{11}H_{11}N_2OCl$•2 HCl: C, 50.99; H, 4.67; N, 10.81. Found: C, 50.90; H, 4.75; N, 10.86.

Example 36

Preparation of 2-(2-(S)-pyrrolidinyl)furo[2,3-b]pyridine hydrochloride

36a. 2-(1-BOC-2-(S)-pyrrolidinyl)furo[2,3-b]pyridine

The compound from step 13b above (0.23 g, 0.7 mmol), triethylamine (0.2 mL, 1.4 mmol), 10% Pd on C (Aldrich, 50 mg) was suspended in 20 mL of EtOH and stirred under H_2 (1 atm), for 4 hours. The mixture was filtered, concentrated and the crude product was purified by flash chromatography on silica gel eluting with hexane/EtOAc (9:1 to 7:3) to provide 140 mg (68%) of the title compound: ^{1}H NMR (DMSO, 120° C, 300 MHz) δ 1.33 (s, 9H), 1.93-2.10 (m, 3H), 2.32 (m, 1H), 3.46-3.53 (m, 2H), 5.0 (m, 1H), 7.28 (dd, 1H, J= 6.7, 2.8 Hz), 8.0 (dd, 1H, J=6.0, 1.7 Hz), 8.22 (dd, J=4.0, 1.4 1H); MS m/z: 289 $(M+H)^+$, 306 $(M+NH_4)^+$.

36b. 2-(2-(S)-pyrrolidinyl)furo[2,3-b]pyridine hydrochloride

The compound from step 36a above (0.13 g, 0.45 mmol) was dissolved in 3 mL of methylene chloride at 0 °C and 3 mL of TFA was added. The reaction mixture was stirred for 1 hour, poured into saturated aqueous K_2CO_3, and extracted with methylene chloride. The organic extract was dried over MgO_4, and the solvent was removed. The residue was chromatographed on silica gel, eluting with 99:1 to 95:5 chloroform:methanol. The residue was treated with a solution of HCl in Et_2O to give 40 mg (42 %) of title compound: ^{1}H NMR (D_2O, 300 MHz) δ 2.15-2.62 (m, 4H), 3.48-3.75 (m, 2H), 5.01 (t, 1H, J=7.8 Hz), 7.11 (s, 1H,), 7.43 (m, 1H, J, 8.18 (dd, 1H, J=7.8, 1.7 Hz) 8.33 (dd, 1H, J=7.8, 4.1, 2.4 Hz). MS m/z: 189 $(M+H)^+$, 206 $(M+NH_4)^+$; Anal. Calcd for $C_{11}H_{12}N_2O$•1.4 HCl: C, 55.22; H, 5.64 N, 11.79. Found: C, 55.11; H, 5.41 N, 11.59

Example 37

Preparation of 2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-c]pyridine dihydrochloride

37a. 2-(1-BOC-2-(S)-pyrrolidinyl)furo[3,2-2]pyridine

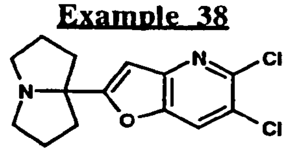
A sample of the compound from step 1c above (1.95 g 12 mmol) was dissolved in 15 mL of DMF, and dpppPdCl$_2$ (0.6 mmol), CuI (0.74 mmol) and triethylamine (14.3 mmol) were added. The mixture was stirred at room temperature for 1 hour, then 2.65 g

(12 mmol) of 4-iodo-3-hydroxypyridine was added. The reaction mixture was stirred at 60 °C for 16 hours. The solution was cooled, diluted with toluene, and the volatiles removed in vacuo. The residue was dissolved in 1 N aqueous HCl, and this solution was washed with ether. The acidic solution was adjusted to a pH 10 with K_2CO_3, and this solution was extracted with methylene chloride. The methylene chloride extract was washed with 20% NaOH, dried over MgO_4, and evaporated. The residue was chromatographed on silica gel, eluting with 100:0 to 95:5 hexane:EtOAc to give 1.64 g (59 %) of title compound: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.30-1.50 (m, 9H), 1.90-2.20 (m, 4H), 2.95-3.15 (m, 2H), 5.05 (m, 1H), 6.55 (br s, 1H) 7.38 (d, 1H, J=8 Hz), 8.45 (bs, 1H), 8.85 (br s, 1H); MS m/z: 289 $(M+H)^+$.

37b 2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-c]pyridine dihydrochloride

A 580 mg sample of the compound from step 37a above was dissolved in an aqueous solution of 37% formaldehyde (8 mL) and 88% formic acid (4 mL) and heated at reflux for 1 hour. The solution was cooled, diluted with water, and adjusted to pH 10 with K_2CO_3. The mixture was extracted with methylene chloride, and the extract dried and concentrated. The residue was purified by chromatography on silica gel, eluting with 100:0 to 97:3 chloroform:methanol. The product was dissolved in ethanol at ambient temperature and a solution of hydrochloric acid in diethyl ether was added dropwise. The resultant white precipitate was then collected by evaporation of solvent and triturated with three portions of diethyl ether to give the title compound (552 mg, 70 %): ^1H NMR (D_2O, 300 MHz) δ 2.20(br s 2H), 2.38-2.57 (m, 3H), 2.85 (br s, 3H), 3.26 (br s, 1H), 3. 85 (br s, 1H), 7.44 (s, 1H), 7.98 (d, 1H, J=6.8 Hz), 8.56 (d, 1H, J=2.3 Hz), 9.10 (s, 1H,); MS m/z; 203 $(M+H)^+$; Anal. Calcd for $C_{12}H_{14}N_2O$•2.0 HCl•0.2 H_2O•0.2 ethanol: C, 51.72; H, 6.16 N, 9.73. Found: C, 51.86; H, 6.13; N, 9.54.

Example 38



Preparation of 2-(Hexahydro-1H-7a-pyrrolizinyl)-5,6-dichlorofuro[3,2-b]pyridine hydrochloride

38a. 5,6-Dichloro-2-(hexahydro-1H-7a-pyrrolizinyl)furo[3,2-b]pyridine

5,6-Dichloro-3-hydroxy-2-iodopyridinol (163 mg, 0.56 mmol), copper(I) iodide (20 mg, 0.10 mmol), bis(triphenylphosphine)palladium(II) chloride (20 mg, 0.030 mmol) and triethylamine (176 mL, 0.67 mmol) were combined and allowed to stir for 1 hour at ambient temperature. 7a-Ethynyl-hexahydro-1H-pyrrolizine (91 mg, 0.67 mmol) in DMF (1.0 mL) was added to the reaction mixture which was then heated to 60°C for 18 hours. After cooling to ambient temperature, 2 *N* aqueous HCl was added and the mixture washed

with Et_2O (2X), basified with 15% NaOH solution and extracted with CH_2Cl_2 (2X). The CH_2Cl_2 phases were combined, dried (MgO_4), concentrated and the residue chromatographed (silica gel; EtOAc/hexane, 1:3) to afford a white solid (116 mg, 70%): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.83-1.97 (m, 6H), 2.20-2.31 (m, 2H), 2.67-2.77 (m, 2H), 3.18-3.25 (m, 2H), 6.71 (s, 1H), 7.78 (s, 1H); MS (CI/NH_3) m/z: 297 $(M+H)^+$.

38b. 5,6-Dichloro-2-(hexahydro-1H-7a-pyrrolizinyl)furo[3,2-b]pyridine hydrochloride

5,6-Dichloro-2-(hexahydro-1H-7a-pyrrolizinyl)furo[3,2-b]pyridine (108 mg, 0.36 mmol) was dissolved in Et_2O (7 mL) and a saturated solution of HCl in Et_2O was added dropwise. The solvent was removed and the product recrystallized from $MeOH/Et_2O$ to afford a white solid (88.5 mg, 74%): mp 229-231 °C; ^1H NMR (D_2O, 300 MHz) δ 2.28-2.95 (m, 6H), 2.75-2.83 (m, 2H), 3.35-3.45 (m, 2H), 3.75-3.83 (m, 2H), 7.27 (s, 1H), 8.24 (s, 1H); MS (CI/NH_3) m/z: 297 $(M+H)^+$; Anal. Calcd for $C_{14}H_{14}Cl_2N_2O \cdot 1.5\ HCl \cdot 0.5\ H_2O$: C, 46.60; H, 4.61; N, 7.76. Found: C, 46.74; H, 5.00; N, 7.67.

Example 39

Preparation of 5,6-Dichloro-2-(2-(R)-pyrrolidinyl)furo[3,2-b]pyridine hydrochloride

39a. 5,6-Dichloro-2-(1-t-butyloxycarbonyl-2-(R)-pyrrolidinyl)furo[3,2-b]pyridine

5,6-Dichloro-2-iodo-3-pyridinol (632 mg, 2.2 mmol), copper(I) iodide (75 mg, 0.40 mmol), bis(triphenylphosphine)palladium(II) chloride (77 mg, 0.11 mmol) and triethylamine (370 mL, 2.6 mmol) were combined in DMF (2.7 mL) and allowed to stir for 1 hour. 1-t-Butyloxycarbonyl-2-(R)-ethynylpyrrolidine (510 mg, 2.6 mmol) in DMF (1 mL) was added and the reaction heated to 60 °C for 16 hours. After cooling to ambient temperature, the mixture was poured over Et_2O/saturated K_2CO_3 solution and the phases separated. The organic phase was washed with brine:water (1:1) (4X), dried ($MgSO_4$) and concentrated. The residue was chromatographed (silica gel; EtOAc/hexane, 1:6) to afford an amber oil (365 mg, 46%): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.32 and 1.45 (two br s, 9H), 1.95-2.40 (m, 4H), 3.45-3.74 (m, 2H), 4.92-5.13 (m, 1H), 6.62 (s, 1H), 7.81 (s, 1H); MS (CI/NH_3) m/z: 357 $(M+H)^+$.

39b. 5,6-Dichloro-2-(2-(R)-pyrrolidinyl)furo[3,2-b]pyridine

5,6-Dichloro-2-(1-t-butyloxycarbonyl-2-(R)-pyrrolidinyl)furo[3,2-b]pyridine (355 mg, 1.0 mmol) was dissolved in CH_2Cl_2 (3 mL) and TFA (3 mL) was added at ambient temperature. After stirring for 1 hour, the solvent was removed and the residue redissolved in CH_2Cl_2 and washed with saturated K_2CO_3 solution, dried ($MgSO_4$) and concentrated. The crude product was chromatographed (silica gel; $CHCl_3$/MeOH, 98:2) to afford a solid (220 mg, 87%): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.81-2.05 (m, 3H), 2.15-2.29 (m, 1H), 3.04-3.20 (m, 2H), 4.39-4.42 (m, 1H), 6.70 (s, 1H), 7.80 (s, 1H); MS (CI/NH_3) m/z: 257 $(M+H)^+$.

39c. 5,6-Dichloro-2-(2-(R)-pyrrolidinyl)furo[3,2-b]pyridine hydrochloride

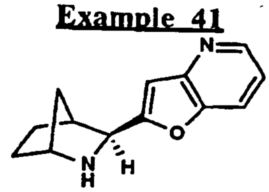
5,6-Dichloro-2-(2-(R)-pyrrolidinyl)furo[3,2-b]pyridine (120 mg, 0.47 mmol) was slurried in Et_2O (5 mL) and a saturated solution of HCl in Et_2O was added dropwise. The solvent was removed and the product recrystallized from MeOH/Et_2O to afford short white needles (86 mg, 63%): mp >260 °C; $[\alpha]_D^{20}$ -4.5 (c 0.51, MeOH); ^1H NMR (D_2O, 300 MHz) δ 2.18-2.65 (m, 4H), 3.51-3.56 (m, 2H), 5.05 (dd, J=8, 8 Hz, 1H), 7.16 (d, J=1 Hz, 1H), 8.24 (d, J=1 Hz, 1H); MS (CI/NH_3) m/z: 257 $(M+H)^+$; Anal. Calcd for $C_{11}H_{10}Cl_2N_2O$•HCl: C, 45.00; H, 3.78; N, 9.54. Found: C, 45.01; H, 3.71; N, 9.48. $[\alpha]_D^{23}$

Example 40

Preparation of 5,6-Dichloro-2-(1-methyl-2-(R)-pyrrolidinyl)furo[3,2-b]pyridine hydrochloride

5,6-Dichloro-2-(2-(R)-pyrrolidinyl)furo[3,2-b]pyridine (56 mg, 0.22 mmol) was dissolved in an aqueous solution of 37% formaldehyde (excess) and 88% formic acid (excess). The aqueous mixture was heated to 60 °C for 1 hour and then allowed to cool to ambient temperature. The reaction mixture was washed with Et_2O, basified with 15% NaOH solution and extracted with CH_2Cl_2 (2X). The organic phases were combined, dried ($MgSO_4$), concentrated and chromatographed (silica gel; $CHCl_3$/MeOH, 98:2) to afford a solid. The solid was dissolved in Et_2O (10 mL) and a saturated solution of HCl in Et_2O was added dropwise. The solvent was removed and the product recrystallized from MeOH/Et_2O to afford a white solid (31 mg, 46%): mp 244-246 °C; ^1H NMR (D_2O, 300 MHz) δ 2.27-2.37 (m, 2H), 2.47-2.71 (m, 2H), 2.93 (s, 3H), 3.38 (m, 1H), 3.78 (m, 1H), 4.81 (m, partially buried under H_2O peak, 1H), 7.27 (s, 1H), 8.26 (s, 1H); MS (CI/NH_3) m/z: 271 $(M + H)^+$; Anal. Calcd for $C_{12}H_{12}Cl_2N_2O$•HCl: C, 46.85; H, 4.26; N, 9.11. Found: C, 46.53; H, 4.21; N, 8.82.

Example 41



Preparation of 2-((1*R*,4*S*)-2-aza-3-(*S*)-bicyclo[2.2.1]heptyl)-2-furo[3,2-b]pyridine dihydrochloride

41a. Ethyl (1*R*,4*S*)-3-(*S*)-2-azabicyclo[2.2.1]heptanecarboxylate hydrochloride

A suspension of ethyl (1*S*,4*R*)-3-(*S*)-N-(*R*)-(+)-α-methylbenzyl-2-azabicyclo[2.2.1]hept-5-enecarboxylate (2.40 g, 8.80 mmol, prepared according to the method described by L. Stella *et al.*, *Tetrahedron Lett.*, 31:2603 (**1990**)) in ethanol (100

mL) and 20% Pd/C (dry) (1.2 g) was placed under 4 atmosphere of H_2 at room temperature for 12 hours. The reaction mixture was then filtered and concentrated *in vacuo* to give the free base as an oil (1.33 g). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.18 (q, 2H), 3.57 (br. s, 1H), 3.34 (s, 1H), 2.63 (br s, 1H), 2.12 (m, 2H), 1.68-1.28 (m, 5H), 1.28 (t, 3H); MS (CI/NH_3) m/z: 170 $(M+H)^+$. The resultant oil was dissolved in methylene chloride (~ 20 mL) and upon addition of HCl/diethyl ether (~6.25 M) a white solid precipitated. The solid was then recrystallized from $EtOH/Et_2O$ and dried under vacuum at 50 °C to give the title compound (0.94 g, 52%): mp >200 °C.

<u>41b. Ethyl (1*R*,4*S*)-N-BOC-2-aza-3-(*S*)-bicyclo[2.2.1]heptanecarboxylate</u>

To a solution of 41a (5.0 g, 24.4 mmol) in CH_2Cl_2 (100 mL) at room temperature under nitrogen was added NEt_3 (3.4 g, 24.4 mmol) followed by di-*t*-butyldicarbonate (5.8 g, 26.8 mmol). The reaction mixture was quenched after 18 hours by the addition of aqueous pH 4 buffer and extracted with Et_2O (2 x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (2000 g, EtOAc/hexane 1:4; $R_f = 0.45$) to yield the title compound (5.4 g, 82%) as an oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.28 (br d, 1H), 4.18 (m, 2H), 3.78 (d, 1H), 2.67 (br. s, 1H), 1.94 (br d, 1H), 1.80-1.40 (m, 5H), 1.44 (d, 9H), 1.28 (t, 3H); MS (CI/NH_3) m/z: 270 $(M+H)^+$, 287 $(M+NH_4)^+$.

<u>41c. (1*R*,4*S*)-3-(*S*)-(Hydroxymethyl)-N-BOC-2-azabicyclo[2.2.1]heptanemethanol</u>

To a solution of 41b (20.0 g, 74.3 mmol) in THF (100 mL) at 0 °C under nitrogen was added lithium aluminum hydride (5.64 g, 148.5 mmol) slowly. The mixture was stirred for 1.5 hours and then quenched with $Na_2SO_4 \cdot 10H_2O$. Diethyl ether was added and the mixture was stirred for 1 h, filtered through diatomaceous earth and concentrated *in vacuo* to give the title compound (16.9 g, 100%) as a white solid: ^{1}H NMR (CDCl3, 300 MHz) δ 1.25 (d, J=10.5 Hz, 1H), 1.49 (s, 9H), 1.58-1.78 (m, 4H), 2.30 (br d, J=1.8 Hz, 1H), 3.43-3.63 (m, 4H), 4.10 (s, 1H), 4.43 (dd, J=2.4, 2.4 Hz, 1H); MS (CI/NH_3) m/z: 171 (M-*t*-butyl+H)$^+$, 228 $(M+H)^+$.

<u>41d. (1*R*,4*S*)-N-BOC-2-aza-3-(*S*)-bicyclo[2.2.1]heptanal</u>

To a mixture of 41c in DMSO (70 mL) was added a solution of sulfur trioxide pyridine complex (17.63 g, 110.7 mmol) in DMSO (30 mL). The mixture was then stirred for 15 minutes, poured into ice water, and extracted with Et_2O. The organic layer was then washed with saturated $NaHCO_3$, 10% citric acid, H_2O, and brine; dried (MgO_4), and concentrated *in vacuo* to give the title compound as an oil (5.08 g, 60%): ^{1}H NMR (CDCl3, 300 MHz) δ 1.26 (m, 1H), 1.45 (s, 9H), 1.61-1.81 (m, 5H), 2.75 (s, 1H), 3.66 (s, 1H), 4.31 (s, 1H), 9.55 (d, J=2.1 Hz, 1H); MS (CI/NH_3) m/z: 226 $(M+H)^+$, 243 $(M+NH_4)^+$.

41e. (1*R*,4*S*)-3-(*S*)-(2,2-Dibromoethenyl)-N-BOC-2-azabicyclo[2.2.1]heptane

To a solution of triphenylphosphine (29.6 g, 113 mmol) in CH_2Cl_2 (60 mL) under nitrogen at 0 °C was added carbon tetrabromide (14.9 g, 45.2 mmol). The mixture was warmed to room temperature and added slowly a solution of 41d (5.08 g, 22.5 mmol) in CH_2Cl_2 (10 mL). After 5 minutes, the mixture was diluted with Et_2O (50 mL) then filtered through silica gel (EtOAc wash). The filtrate was concentrated and the residue was diluted with EtOAc/hexane (1:4). The resulting precipitate was removed by filtration and the filtrate was concentrated. The resulting residue (9.77 g) was chromatographed (silica gel; Hexane/Et_2O, 95:5; Hexane/EtOAc, 90:10) to afford a solid (4.33 g, 51%): ^1H NMR (CDCl3, 300 MHz) δ 1.32 (br s, 1H), 1.45 (s, 9H), 1.60-1.80 (m, 5H), 2.45 (br s, 1H), 3.83 (d, J=8.1 Hz, 1H), 4.12 (br s, 1H), 6.31 (d, J=8.1 Hz, 1H); MS (CI/NH_3): 382 $(M+H)^+$.

41f. (1*R*,4*S*)-3-(*S*)-(2-Ethynyl)-N-BOC-2-azabicyclo[2.2.1]heptane

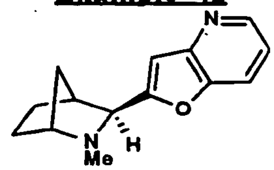
A 2.5 M solution of n-BuLi in hexane (11.4 mL, 28.4 mmol) was added slowly to a solution of 41e (4.33 g, 11.4 mmol) in THF (40 mL) under nitrogen at 0 °C. The mixture was then stirred for 10 minutes, quenched with saturated $NaHCO_3$ and extracted with EtOAc (2X). The combined organic extracts were washed with H_2O and brine, dried (MgO4), and concentrated. The crude oil (2.87 g) was chromatographed (silica gel; Hexane/EtOAc, 90:10) to afford a colorless oil (1.17 g, 46%): ^1H NMR (CDCl3, 300 MHz) δ 1.36-1.42 (m, 3H), 1.50 (s, 9H), 1.66-1.75 (m, 2H), 2.10 (m, 1H), 2.25 (d, J=1.5 Hz, 1H), 2.59 (s, 1H), 3.89 (s, 1H), 4.18 (s, 1H); MS (CI/NH_3): 222 $(M+H)^+$, 239 $(M+NH_4)^+$.

41g. 2-((1*R*,4*S*)-2-aza-3-(*S*)-bicyclo[2.2.1]heptyl)-2-furo[3,2-b]pyridine dihydrochloride

A solution of 2-iodo-3-hydroxypyridine (0.4 g, 1.8 mmol), bis(triphenylphosphine)-palladium(II)chloride (0.06 g, 0.09 mmol), copper (I) iodine (0.05 g, 0.27 mmol), NEt_3 (0.25 mL, 1.8 mmol) in DMF (2 mL) was stirred for 1 hour. Then a solution of 41f (0.4 g, 1.8 mmol) in DMF (0.5 mL) was then added. The mixture was heated at 60 °C for 16, quenched with saturated $NaHCO_3$, and extracted with EtOAc (2X). The combined EtOAc extracts were washed with H_2O and brine, dried (MgO4), and concentrated. The crude solid (0.64 g) was chromatographed (silica gel; hexane/EtOAc, 60:40) to give a yellow colored solid (0.27 g). This was dissolved in CH_2Cl_2 and upon addition of HCl/Et_2O a solid was collected and further purified by heating in MeOH with activated carbon for 15 minutes. After filtering, the MeOH filtrate was concentrated to give the title compound (0.11 g, 22%) as a white solid: mp 182-185 °C; $[\alpha]_D^{23}$ +33.2 (c 0.29, MeOH); ^1H NMR (MeOD, 300 MHz) δ 1.81-2.01 (m, 6H), 2.24-2.28 (br d, J=11.8 Hz, 1H), 3.31 (s, 1H), 4.28 (s, 1H), 7.51 (s, 1H), 7.87 (m, 1H), 8.58 (br d, J=8.5 Hz, 1H), 8.62 (br s, 1H); MS (CI/NH_3) m/z: 215 $(M+H)^+$, 232 $(M+NH_4)^+$; Anal. Calcd for

$C_{13}H_{16}Cl_2N_2O \cdot 0.2\ HCl \cdot 0.5\ H_2O$: C, 51.45; H, 5.71; N, 9.23. Found: C, 51.48; H, 5.72; N, 8.98.

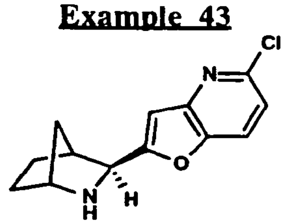
Example 42



Preparation of 2-((1*R*,4*S*)-2-aza-3-(*S*)-bicyclo[2.2.1]heptyl)-2-methyl-2-furo[3,2-b]pyridine dihydrochloride

To a solution of 2-((1*R*,4*S*)-2-aza-3-(*S*)-bicyclo[2.2.1]heptyl)-2-furo[3,2-b]pyridine dihydrochloride (from Example 41, 0.08 g, 0.3 mmol) in EtOH (3.0 mL), formaldehyde (37% w/w aqueous) (5.0 mL) and HOAc (0.2 mL) was added sodium cyanoborohydride (0.08 g, 1.4 mmol). The mixture was stirred for 16 hours, quenched with saturated $NaHCO_3$, and extracted with Et_2O. The organic layer was washed with H_2O, dried ($MgSO_4$) and concentrated. The crude product (0.22 g) was chromatographed (silica gel; EtOH/EtOAc, 10:90) to afford an oil (0.06 g). The oil was dissolved in CH_2Cl_2 and a solution of HCl in Et_2O was added. The solvent was removed and the product was recrystallized from CH_2Cl_2/Et_2O to afford the title compound as a white solid (0.09 g, 100%): mp 225 °C (dec.); $[\alpha]_D^{23}$ +5.4 (c 0.35, MeOH); ^1H NMR (MeOD, 300 MHz) δ 1.84-2.24 (m, 5H), 2.41 (m, 1H), 3.12 (s, 3H), 3.20 (br s, 1H), 4.22 (s, 1H), 4.61 (s, 1H), 7.62 (s, 1H), 7.94 (dd, J=6.0, 6.0 Hz, 1H), 8.73 (dd, J=0.9, 1.2 Hz, 1H), 8.84 (br d, J=6.0 Hz, 1H); MS (CI/NH_3) m/z: 229 $(M+H)^+$, 246 $(M+NH_4)^+$; Anal. Calcd for $C_{14}H_{18}Cl_2N_2O \cdot 0.2\ H_2O$: C, 55.17; H, 6.08; N, 9.19. Found: C, 55.24; H, 5.76; N, 9.05.

Example 43

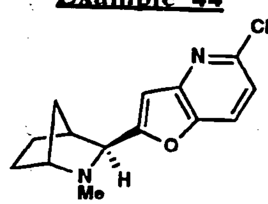


Preparation of 2-((1*R*,4*S*)-2-aza-3-(*S*)-bicyclo[2.2.1]heptyl)-5-chloro-2-furo[3,2-b]pyridine dihydrochloride

A solution of 2-iodo-3-hydroxy-6-chloropyridine (0.46 g, 1.8 mmol), bis(triphenylphosphine)-palladium(II)chloride (0.06 g, 0.09 mmol), copper (I) iodine (0.05 g, 0.27 mmol), NEt_3 (0.25 mL, 1.8 mmol) in DMF (2 mL) was stirred for 1 hour. Then a

solution of (1*R*,4*S*)-3-(*S*)-(2-ethynyl)-*N*-*t*-butylcarboxyl-2-azabicyclo[2.2.1]heptane from Example 41f above (0.40 g, 1.8 mmol) in DMF (0.5 mL) was then added. The mixture was heated at 60 °C for 16 h, quenched with saturated $NaHCO_3$ and extracted with EtOAc. The combined EtOAc extracts was washed with H_2O and brine, dried ($MgSO_4$), and concentrated. The crude product (0.68 g) was chromatographed (silica gel; hexane/EtOAc, 80:20) to give a solid (0.57 g). The solid was dissolved in CH_2Cl_2 and a solution of HCl in Et_2O was added. The solvent was removed and the product was recrystallized form EtOH/Et_2O to afford the title compound as a white solid (0.47 g, 93%): mp >200 °C; $[\alpha]_D^{23}$ +31.2 (c 0.29, MeOH); ^1H NMR (MeOD, 300 MHz) δ 1.77-1.99 (m, 5H), 2.24 (m, 1H), 3.15 (s, 1H), 4.23 (s, 1H), 4.74 (s, 1H), 7.15 (s, 1H), 7.43 (d, J=9.0 Hz, 1H), 8.00 (dd, J=0.9, 0.9 Hz, 1H); MS (CI/NH_3) m/z: 249 $(M+H)^+$; Anal. Calcd for $C_{13}H_{14}Cl_2N_2O$•0.1 HCl: C, 54.06; H, 4.92; N, 9.70. Found: C, 54.21; H, 4.90; N, 9.50.

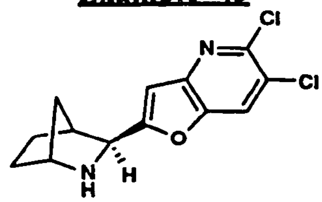
Example 44



Preparation of 2-((1*R*,4*S*)-2-aza-3-(*S*)-bicyclo[2.2.1]heptyl)-5-chloro-2-methyl-2-furo[3,2-b]pyridine dihydrochloride

To a solution of 37% aqueous formaldehyde (12 mL) and 88% formic acid (6 mL) was added 2-((1*R*,4*S*)-2-aza-3-(*S*)-bicyclo[2.2.1]heptyl)-5-chloro-2-furo[3,2-b]pyridine dihydrochloride from Example 43 above (0.4 g, 1.4 mmol). The reaction solution was refluxed for 16 hours. After cooling to ambient temperature, the solution was basified to pH 12 by the addition of solid K_2CO_3, and extracted with EtOAc. The organic extract was washed with H_2O, dried ($MgSO_4$), and concentrated. The crude solid was dissolved in CH_2Cl_2 and a solution of HCl in Et_2O was added. The solvent was removed and the title compound (0.03 g, 22%) was collected as a white solid: mp 197-200 °C; $[\alpha]_D^{23}$ +5.6 (c 0.23, MeOH); ^1H NMR (MeOD, 300 MHz) δ 1.82-2.21 (m, 5H), 2.33-2.38 (m, 2H), 3.08 (s, 3H), 3.13 (br s, 1H), 4.16 (s, 1H), 4.45 (s, 1H), 7.23 (s, 1H), 7.43 (d, J=8.7 Hz, 1H), 8.04 (dd, J=0.9, 1.2 Hz, 1H); MS (CI/NH_3) m/z: 263 $(M+H)^+$; Anal. Calcd for $C_{14}H_{17}Cl_3N_2O$•0.2 HCl•0.9 H_2O: C, 46.82; H, 5.33; N, 7.80. Found: C, 46.76; H, 5.34; N, 7.47.

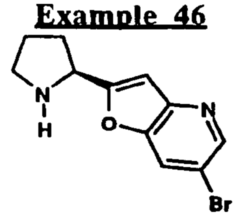
Example 45



Preparation of 2-((1*R*,4*S*)-2-aza-3-(*S*)-bicyclo[2.2.1]heptyl)-5,6-dichloro-2-furo[3,2-b]pyridine dihydrochloride

A solution of 2-iodo-3-hydroxy-5,6-dichloropyridine (0.45 g, 1.6 mmol), bis(triphenylphosphine)-palladium(II)chloride (0.06 g, 0.08 mmol), copper (I) iodine (0.05 g, 0.24 mmol), NEt_3 (0.22 mL, 1.6 mmol) in DMF (1.5 mL) was stirred for 1 hour. Then a solution (1*R*,4*S*)-3-(*S*)-(2-ethynyl)-*N*-*t*-butylcarboxyl-2-azabicyclo[2.2.1]heptane from Example 41f above (0.4 g, 1.8 mmol) in DMF (1.0 mL) was added. The mixture was heated at 60 °C for 16 hours, quenched with saturated $NaHCO_3$ and extracted with EtOAc (2X). The combined EtOAc extracts was washed with H_2O, brine, dried ($MgSO_4$), and concentrated. The crude solid (0.60 g) was chromatographed (silica gel; Hexane/EtOAc, 80:20) to give a solid (0.2 g). The solid was then dissolved in CH_2Cl_2 and a solution of HCl in Et_2O was added. The solvent was removed and the product was recrystallized from EtOH/Et_2O to afford a white solid (23 mg, 5.1%): mp >200 °C; ^1H NMR (MeOD, 300 MHz) δ 1.74-1.99 (m, 5H), 2.20-2.25 (m, 1H), 3.15 (s, 1H), 4.23 (s, 1H), 4.74 (s, 1H), 7.19 (d, J=0.6 Hz), 8.30 (s, 1H); MS (CI/NH_3) m/z: 283 $(M+H)^+$, 300 $(M+NH_4)^+$; Anal. Calcd for $C_{13}H_{12}Cl_2N_2O$•0.6 EtOH•0.8 HCl: C, 50.17; H, 4.86; N, 8.24. Found: C, 50.12; H, 4.78; N, 8.15.

Example 46



Preparation of 6-bromo-2-(2-(S)-pyrrolidinyl)furo[3,2-b]pyridine dihydrochloride

46a. 2-(1- BOC-2-(S)-pyrrolidinyl)-6-bromofuro[3,2-b]pyridine

A sample of 5-bromo-3-pyridinol (2.06 g, 11.8 mmol) and Na_2CO_3 (3.65 g, 2.1 mmol) were dissolved in H_2O (25 mL). To this solution was added I_2 (3.0 g, 12 mmol), and the reaction mixture was stirred overnight. The mixture was then poured slowly into 2 M aqueous HCl, and the acidity was adjusted to pH 3. The product was collected by filtration and crystallized from ethanol/ether, affording title compound (2.92 g, 83%): MS

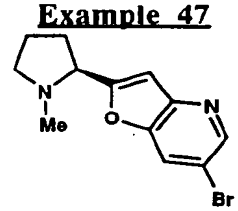
(CI/NH_3) m/e: 300 $(M+H)^+$, 317 $(M+NH_4)^+$; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25 (d, J=2 Hz, 1H), 7.93 (d, J=2 Hz, 1H).

A sample of 5-bromo-2-iodo-3-pyridinol (0.60 g, 2.0 mmol), from above, was dissolved in DMF (3 mL), and $Pd(PPh_3)_2Cl_2$ (0.07 g, 0.1 mmol), CuI (0.077 g, 0.4 mmol) and triethylamine (0.33 mL, 2.4 mmol) were added. The mixture was stirred under N_2 at room temperature for 1 hour, then 1-BOC-2-(S)-ethynylpyrrolidine (0.429 g, 2.2 mmol), from Example 1c above, dissolved in DMF (1 mL), was added carefully. The reaction mixture was stirred at 60 °C for 16 hours, then cooled to room temperature. The reaction mixture was diluted with ether, then washed with 10% NaOH and brine. The organic extract was dried over $MgSO_4$ and concentrated. The residue was chromatographed (silica gel; hexane/ethyl acetate, 5:1 to 2:1) to give the title compound (0.32 g, 43%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.32, 1.46 (2 s, 9H), 1.91-2.40 (m, 4H), 3.37-3.70 (m, 2H), 4.93-5.15 (m, 1H), 6.66 (s, 1H), 7.85 (s, 1H), 8.55 (s, 1H); MS (CI/NH_3) m/z: 367, 369 $(M+H)^+$.

46b. 6-bromo-2-(2-(S)-pyrrolidinyl)furo[3,2-b]pyridine dihydrochloride

A sample of the compound (0.14 g, 0.38 mmol) from step 46a above was dissolved in a solution of hydrogen chloride in dioxane (4 N, 3 mL) and cooled to 0 °C. After stirring at room temperature for 16 hours, the solvent was evaporated under reduced pressure. The residue was then triturated with ether several times to give the hydrochloride salt as a white solid (0.119g, 92%): $[\alpha]_D^{23}$ +4.09 (c 0.45, MeOH); ^{1}H NMR (D_2O, 300 MHz) δ 2.14-2.50 (m, 3H), 2.59 (m, 1H), 3.50-3.55 (m, 2H), 5.07 (t, 1H, J=7.7 Hz), 7.22 (t, J=0.7 Hz, 1H), 8.32 (dd, J=0.7, 1.8 Hz, 1H), 8.66 (d, 1H, J=1.8 Hz); MS (CI/NH_3) m/z: 267, 269 $(M+H)^+$; Anal. Calcd for $C_{11}H_{11}N_2OBr{\cdot}2.2HCl$: C, 38.04; H, 3.83; N, 8.07. Found: C, 38.01; H, 3.75; N, 7.92.

Example 47

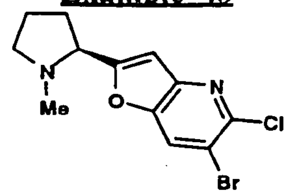


Preparation of 6-bromo-2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine dihydrochloride

A sample of 2-(1- BOC-2-(S)-pyrrolidinyl)-6-chlorofuro[3,2-b]pyridine (180 mg, 0.49 mmol), from Example 46a above, was dissolved in 1.5 mL of 88% formic acid and 3 mL of 37% aqueous formaldehyde and heated at 100 °C for 16 hours. The reaction mixture was cooled to ambient temperature, poured into saturated aqueous K_2CO_3, and extracted with methylene chloride. The organic extract was dried over $MgSO_4$, and the solvent was removed. The residue was chromatographed (silica gel; EtOAc/MeOH, 10:1) to give the amine as colorless oil (92 mg, 67%). The amine was converted to the hydrochloride salt by

treatment with HCl/ether, and the salt was recrystallized from ethanol/ethyl acetate to give the title compound (68 mg, 61%) as a white solid: ^{1}H NMR (D_2O, 300 MHz) δ 2.20-2.40 (m, 2H), 2.46-2.80 (m, 3H), 3.00 (br s, 3H), 3.38 (m, 1H), 3.88 (m, 1H), 7.32 (s, 1H), 8.31 (dd, J=0.7, 1.8 Hz, 1H), 8.67 (d, J=1.8 Hz, 1H); MS (CI/NH_3) m/e: 281 $(M+H)^+$, 283 $(M+2H)^+$; Anal. Calcd for $C_{12}H_{13}N_2OBr{\cdot}1.8HCl$: C, 41.56; H, 4.30; N, 8.08. Found: C, 41.60; H, 4.12; N, 7.89. $[a]_D$ -2.8 (c 0.20, MeOH)

Example 48



Preparation of 6-bromo-5-chloro-2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine dihydrochloride

48a. 2-(1-BOC-2-(S)-pyrrolidinyl)-5-chloro-6-bromofuro[3,2-b]pyridine

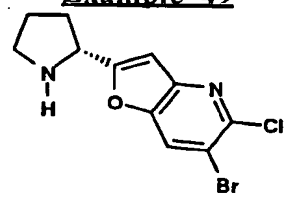
5-Bromo-6-chloro-3-hydroxy-2-iodopyridine (2.0 g, 6.0 mmol), palladium (II) bis(triphenylphosphine) chloride (0.21 g, 0.30 mmol), CuI (0.228 g, 1.2 mmol) and triethylamine (1.0 mL) were dissolved in DMF (8 mL). After stirring at room temperature for 1 hours, the N-Boc-2-(R)-pyrrolidinyl-acetylene (1.40 g, 7.2 mmol) was added and the resultant mixture was stirred at room temperature for 16 hours. Ethyl acetate was added to the reaction mixture. DMF was removed by washing with H_2O: brine (1:1, 3X). The organic layer was dried, concentrated and chromatographed (silica gel; hexane/EtOAc, 10:1 to 5:1) to afford the title compound as colorless oil (170 mg, 11%): ^{1}H NMR ($CDCl_3$, 300MHz) δ 1.31 (s, 5H), 1.46 (s, 4H), 1.8-1.95 (m, 2H), 1.96-2.23 (m, 2H), 3.32-3.58 (m, 2H), 4.15-4.41 (m, 1H), 6.60 (s, 1H), 7.95 (s, 1H); MS (CI/NH_3) m/z: 403 $(M+H)^+$.

48b. 6-bromo-5-chloro-2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine dihydrochloride

A sample of 2-(2-(S)-pyrrolidinyl)-5-chloro-6-bromofuro[3,2-b]pyridine (170 mg, 0.42 mmol), from Example 48a above, was dissolved in 1.0 mL of 88% formic acid and 3 mL of 37% aqueous formaldehyde and heated at 100 °C for 16 hour. The reaction mixture was cooled, poured into saturated aqueous K_2CO_3, and the mixture was extracted with methylene chloride. The extract was dried over $MgSO_4$, and the solvent was removed. The residue was chromatographed (silica gel; hexane/EtOAc, 5:1 to 1:1) to give the amine as colorless oil (60 mg, 45%). The amine was converted to the hydrochloride salt by treatment with HCl/ether, and the salt was recrystallized from ethanol/ethyl acetate to give the title compound (50 mg, 71%): mp 250-253 °C; $[\alpha]_D^{23}$ -28.3 (c, 0.35, MeOH); ^{1}H NMR (D_2O, 300MHz) δ 2.26-2.38 (m, 2H), 2.47-2.72 (m, 2H), 2.93 (s, 3H), 3.41 (m, 1H),

3.78 (m, 1H), 7.27 (s, 1H), 8.40 (s, 1H); MS (CI/NH_3) m/z: 315$(M+H)^+$; Anal. Calcd for $C_{12}H_{12}N_2OBrCl \cdot 1HCl$: C, 40.94; H,3.72; N,7.96. Found: 40.76; H, 3.76; N, 7.79.

Example 49



Preparation of 6-bromo-5-chloro-2-(2-(R)-pyrrolidinyl)furo[3,2-b]pyridine hydrochloride

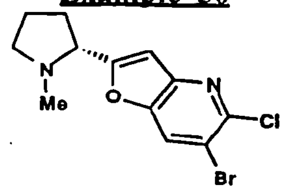
49a. 2-(1-BOC-2-(R)-pyrrolidinyl)-5-chloro-6-bromofuro[3,2-b]pyridine

5-Bromo-6-chloro-3-hydroxy-2-iodopyridine (4.0 g, 12.0 mmol), palladium (II) bis(triphenylphosphine) chloride (0.42 g, 0.60 mmol), CuI (0.456 g, 2.4 mmol) and triethylamine (2.0 mL) were mixed in DMF at room temperature. The mixture was stirred at room temperature for an hour, the N-Boc-2-(R)-pyrrolidinyl-acetylene (2.56 g, 13.2 mmol) was added. The mixture was heated at 55 °C over two nights. After cooling to room temperature, Et_2O (20 mL) was added and the mixture was washed with H_2O: Brine (1:1, 3X). The organic layer was dried, concentrated and chromatographed (silica gel; Hexane/EtOAc, 10:1 to 5:1) to afford the title compound as an oil (2.71 g, 56%): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.31, 1.46 (s, 9H), 1.95-2.06 (m, 2H), 2.06-2.20 (m, 1H), 2.20-2.35 (m, 1H), 3.42-3.70 (m, 2H), 4.95, 5.07 (br s, 1H), 6.60 (s, 1H), 7.95 (s, 1H); MS (CI/NH_3) m/z: 403 $(M+H)^+$.

49b. 6-bromo-5-chloro-2-(2-(R)-pyrrolidinyl)furo[3,2-b]pyridine hydrochloride

To a sample of the compound from step 49a above was added a 4.0 M solution of HCl in dioxane. After stirring for 12 hours, the solvent was evaporated. The white solid was triturated with Et_2O and dried under vacuum to afford the hydrochloride salt: mp >250° C; $[\alpha]_D^{23}$ -4.83 (c 0.14, MeOH); ^1H NMR (D_2O, 300 MHz) δ 2.20-2.50 (m, 3H), 2.5-2.65 (m, 1H), 3.51 (t, J=6.9 Hz, 2H), 5.04 (t, J=18.0 Hz, 1H), 7.15 (s, 1H), 8.39 (s, 1H); MS (CI/NH_3) m/z: 301 $(M+H)^+$; Anal. Calcd for $C_{10}H_{11}N_2OClBr \cdot HCl$: C, 39.09; H, 3.28: N, 8.29. Found: C, 39.12; H, 3.54; N, 7.91.

Example 50



Preparation of 6-bromo-5-chloro-2-(1-methyl-2-(R)-pyrrolidinyl)furo[3.2-b]pyridine hydrochloride

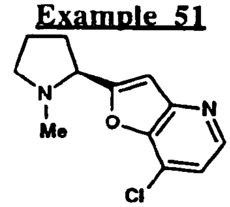
50a. 2-(1-methyl-2-(R)-pyrrolidinyl)-5-chloro-6-bromofuro[3,2-b]pyridine

A sample of the compound from step 49a above (0.355 g, 0.88 mmol) in 88% formic acid (5.0 mL) and 37% aqueous formaldehyde (10 mL) was heated at 70 °C for two hours. After cooling to room temperature, the solution was basified to pH 9 with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3X). The combined organic extracts were dried, concentrated and chromatographed (silica gel; CH_2Cl_2/MeOH, 10:0.2 to 10:0.5) to afford an oil (0.226 g, 81%): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.80-1.97 (m 1H), 2.00-2.15 (m, 2H), 2.20-2.28 (m, 1H), 2.33 (s, 3H), 3.20-3.30 (m, 1H), 3.42-3.48 (m, 1H), 4.70-4.75 (m, 1H), 6.72 (s, 1H), 7.98 (s, 1H); MS (CI/NH_3) m/z: 315 $(M+H)^+$.

50b. 6-bromo-5-chloro-2-(1-methyl-2-(R)-pyrrolidinyl)furo[3,2-b]pyridine hydrochloride

To an ethereal solution of the compound from step 50a at room temperature was added a 1.0 M solution of HCl in Et_2O dropwise until precipitation ceased. The solvent was removed, and the white solid was triturated with Et_2O then dried under vacuum to afford the title compound: mp 246-248 °C; $[\alpha]_D^{23}$ +32.65 (c 0.68, MeOH); ^1H NMR (D_2O, 300 MHz) δ 2.25-2.40 (m, 2H), 2.46-2.70 (m, 2H), 2.94 (s, 3H), 3.35-3.44 (m, 1H), 3.78-3.84 (m, 1H), 4.80-4.85 (m, 1H), 7.27 (s, 1H), 8.40 (s, 1H); MS (CI/NH_3) m/z: 315$(M+H)^+$; Anal. Calcd for $C_{12}H_{12}N_2OBrCl \cdot 1.1HCl \cdot 0.3H_2O$: C, 39.91; H, 3.82; N,7.76. Found: 40.26; H, 4.00; N, 7.39.

Example 51



Preparation of 7-chloro-2-(1-methyl-2-(S)-pyrrolidinyl)furo[3.2-b]pyridine hydrochloride

51a. 2-(1-BOC-2-(S)-pyrrolidinyl)-7-chloro-furo[3,2-b]pyridine

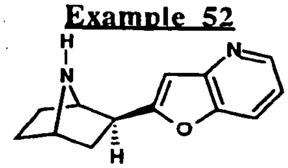
To a solution of 2-iodo-4-chloro-3-hydroxypyridine (1.04 g, 4.10 mmol) in DMF (10 mL) was added dpppPdCl2 (0.140 g, 0.20 mmol), CuI (0.152 g, 0.80 mmol) and Et_3N (0.496 g, 4.90 mmol). The mixture was stirred at room temperature for one hour. A

solution of 1-Boc-2-(S)-ethynylpyrrolidine (0.80 g, 4.10 mmol), from step 1c above, in DMF (10 mL) was added and the mixture was heated at 60 °C for 16 hours. The reaction mixture was cooled to room temperature and poured into saturated $NaHCO_3$ and washed with Et_2O (4X 100mL). The combined organic extracts were washed with brine/H_2O (1/1 400mL), dried ($MgSO_4$), and concentrated . The crude product was chromatographed (silica gel; CH_2Cl_2/MeOH, 90:10) to afford the title compound as a brown oil (0.180 g, 14%): ^1H NMR ($CDCl_3$, 300MHz) δ 1.40 (s, 9H), 1.95-2.10 (m, 4H), 3.10-3.25 (m, 2H), 4.90-5.10 (m, 1H), 6.65 (s, 1H), 7.10 (br s, 1H), 8.38 (br s, 1H); MS (DCI/NH_3) m/z: 323 $(M+H)^+$.

51b. 7-chloro-2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine hydrochloride

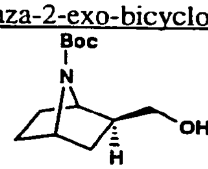
A solution of 2-(1-BOC-2-(S)-pyrrolidinyl)-7-chlorofuro[3,2-b]pyridine, from step 51a above, in HCO_2H (15.0 mL, 88%) and H_2CO (15mL, 37%) was refluxed for one hour. After cooling to room temperature and the solution was acidified to pH=2.0 with 1 N aqueous HCl and washed with Et_2O (150 mL). The aqueous layer was basified with 15% NaOH and extracted with CH_2Cl_2 (4X 400mL). The combined CH_2Cl_2 extracts were dried ($MgSO_4$) and concentrated. The crude material was chromatographed (silica gel; CH_2Cl_2:MeOH, 95:5) to afford the title compound as a light yellow oil (0.036 g, 15%). The amine was dissolved in Et_2O and cooled to 0 °C and a saturated solution of HCl in Et_2O was added until precipitation ceased. The solvent was removed and the yellow solid was placed under vacuum to afford the title compound: $[\alpha]_D^{23}$ +26.24 (c 0.05 H_2O); ^1H NMR (D_2O, 300 MHz) δ 2.28-2.42 (m, 2H), 2.50-2.68 (m, 2H), 2.98 (s, 3H), 3.42 (br s, 1H), 3.62 (br s, 1H), 4.83-4.95 (m, 1H), 7.38 (s, 1H), 7.59 (d, J=6.0 Hz, 1H), 8.44 (d, J=6.0 Hz, 1H); MS (DCI/NH_3) m/z: 237 $(M+H)^+$; Anal. Calcd for $C_{12}H_{13}N_2O\cdot1.2$ $HCl\cdot0.10H_2O\cdot0.20Et_2O$: C, 51.75; H, 5.56; N, 9.43. Found C, 51.40; H, 5.49; N,9.03.

Example 52



(±)-2-(7-aza-2-exo-bicyclo[2.2.1]heptyl)furo[3,2-b]pyridine dihydrochloride

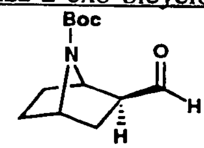
52a. (±)-7-(*tert*-butoxycarbonyl)-7-aza-2-exo-bicyclo[2.2.1]heptanemethanol



A solution of the exo-substituted ester (12.3 g, 48.1 mmol, prepared according to the procedure of Hernandez *et al.*, *J. Org. Chem.*, 60:2683-2691 (**1995**)) in THF (40 mL) was added to a suspension of lithium aluminum hydride (4.38 g, 115 mmol) in THF (120

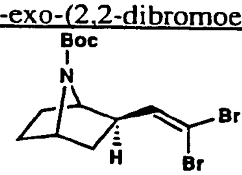
mL) at -10 °C. After 30 minutes, the reaction was quenched by the careful addition of solid $Na_2SO_4 \cdot 10H_2O$ until gas evolution ceased. The mixture was diluted with Et_2O and some Celite was added. The mixture was stirred at ambient temperature for 1 hour then the solids were removed by filtration through a pad of Celite and anhydrous Na_2SO_4. Concentration of the filtrate afforded the title compound as a colorless oil (10.3 g, 94%): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.23-1.55 (m, 3H), 1.45 (s, 9H), 1.75-1.82 (m, 2H), 1.88-1.94 (m, 2H), 3.38-3.44 (m, 2H), 4.14-4.22 (m, 2H); MS (CI/NH_3) m/z: 228 $(M+H)^+$, 245 $(M+NH_4)^+$.

52b. (±)-7-(*tert*-butoxycarbonyl)-7-aza-2-exo-bicyclo[2.2.1]heptanecarboxaldehyde



To solution of oxalylchloride (4.73 mL, 54.2 mmol) in CH_2Cl_2 (200 mL) at -78 °C was added methyl sulfoxide (7.70 mL, 108 mmol). After 10 minutes, a solution of (±)-7-(*tert*-butoxycarbonyl)-2-exo-(hydroxymethyl)-7-azabicyclo[2.2.1]heptane, from step 52a above, in CH_2Cl_2 (25 mL) was added. After 15 minutes, triethylamine (31.5 mL, 226 mmol) was added. The reaction mixture was stirred at -78 °C for 30 minutes, then warmed to -40 °C over a 30 minute period. The reaction was quenched by the addition of saturated aqueous NH_4Cl, warmed to ambient temperature, and extracted with CH_2Cl_2 (2X). The combined organic extracts were dried (Na_2SO_4) and concentrated to afford the title compound as a pale yellow oil (9.82 g, 96%): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.42 (s, 9H), 1.39-1.60 (m, 3H), 1.84 (m, 1H), 2.20 (m, 1H), 2.50 (m, 1H), 3.09 (M, 1H), 4.29 (br s, 1H), 4.53 (br s, 1H), 9.64 (d, J=2.0 Hz, 1H); MS (CI/NH_3) m/z: 226 $(M+H)^+$, 243 $(M+NH_4)^+$.

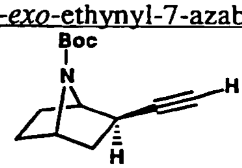
52c. (±)-7-(*tert*-butoxycarbonyl)-2-exo-(2,2-dibromoethenyl)-7-azabicyclo[2.2.1]heptane.



Carbon tetrabromide (28.9 g, 87.2 mmol) was added to a 0 °C solution of triphenyphosphine (57.2 g, 218 mmol) in CH_2Cl_2 (200 mL) under a nitrogen atmosphere. The solution was warmed to ambient temperature, stirred for 10 minutes, then a solution of the aldehyde from step 52b in CH_2Cl_2 (20 mL0 was added via cannula. After 15 minutes, the reaction mixture was diluted with 1:1 EtOAc/hexane (300 mL) and filtered through a pad of Celite and silica gel (1:1 EtOAc/hexane wash). The filtrate was concentrated and the residue was purified by chromatography (silica gel; hexane/EtOAc 90:10) to afford the title compound as a colorless oil (12.8 g, 77%): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.46 (s, 9H), 1.38-1.60 (m, 3H), 1.70-1.86 (m, 3H), 2.56 (dt, J=4.4, 8.8 Hz, 1H), 4.05 (br s, 1H),

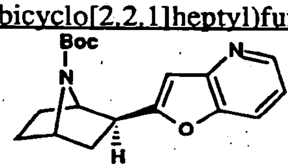
4.24 (br s, 1H), 6.39 (d, J=8.8 Hz, 1H); MS (CI/NH_3) m/z: 382 $(M+H)^+$, 399 $(M+NH_4)^+$.

52d. (±)-7-(*tert*-butoxycarbonyl)-2-*exo*-ethynyl-7-azabicyclo[2.2.1]heptane



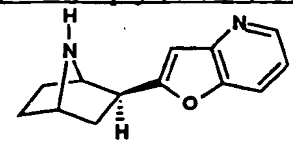
To a solution of the vinyl dibromide (12.8 g, 33.7 mmol), from step 52c above, in THF (170 mL) at -78 °C was added a 2.5 M solution of n-butyllithium in hexane (27.6 mL, 69.0 mmol). The reaction was quenched after 15 minutes at -78 °C by the addition of saturated aqueous NH_4Cl and warmed to ambient temperature. The mixture was extracted with EtOAc (2X). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Purification of the residue by chromatography (silica gel; hexane/EtOAc 80:20) afforded the title compound as a colorless oil (6.95 g, 93%): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.24-1.48 (m, 2H), 1.46 (s, 9H), 1.64-1.92 (m, 4H), 2.09 (d, J=2.4 Hz, 1H), 2.50 (m, 1H), 4.32 (br s, 2H); MS (CI/NH_3) m/z: 222 $(M+H)^+$, 239 $(M+NH_4)^+$.

52e. (±)-2-(7-BOC-7-aza-2-*exo*-bicyclo[2.2.1]heptyl)furo[3,2-b]pyridine



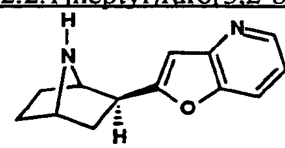
3-Hydroxypyridine (366 mg, 1.65 mmol), copper(I) iodide (47 mg, 0.25 mmol), bis(triphenylphosphine)palladium(II) chloride (58 mg, 0.083 mmol) and triethylamine (242 mL, 1.74 mmol) were combined in DMF (3.0 mL) and allowed to stir for 1 hour. A solution of (±)-7-(*tert*-Butoxycarbonyl)-2-exo-ethynyl-7-azabicyclo[2.2.1]heptane (366 mg, 1.65 mmol), from step 52d, in DMF (1 mL) was added and the reaction mixture heated to 60°C for 12 hours then 80 °C for 4 hours. After cooling to ambient temperature, the mixture was diluted with 15% NaOH and extracted with Et_2O (3X). The combined organic extracts were dried ($MgSO_4$), concentrated and purified by chromatography (silica gel; EtOAc/hexane, 50:50) to afford the title compound as a white solid (362 mg, 70%): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.24 (br s, 9H), 1.38-1.64 (m, 2H), 1.79-2.01 (m, 3H), 2.13 (m, 1H), 3.15 (dd, J=5.3, 8.6 Hz, 1H), 4.42 (br s, 1H), 4.50 (br s, 1 H), 6.64 (s, 1H), 7.14 (dd, J=5.4, 8.2 Hz, 1H), 7.64 (d, J=8.2 Hz, 1H), 8.48 (d, J=5.4 Hz, 1H); MS (CI/NH_3) m/z: 315 $(M + H)^+$.

52f. (±)-2-(7-aza-2-*exo*-bicyclo[2.2.1]heptyl)furo[3,2-b]pyridine



The compound from step 52e above (330 mg, 1.05 mmol) was dissolved in CH_2Cl_2 (3 mL) and TFA (3 mL) added at ambient temperature. After stirring for 30 minutes, the solvent was removed and the residue diluted with CH_2Cl_2 and washed with saturated K_2CO_3 solution, dried ($MgSO_4$) and concentrated. The crude product was chromatographed (silica gel; $CHCl_3$/MeOH/NH_4OH, 90:10:0.1) to afford the amine as a light yellow oil (223 mg, 99%): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.40-1.58 (m, 2H), 1.66-2.14 (m, 6H), 3.15 (dd, J=5.4, 9.3 Hz, 1H), 3.83 (br s, 2H), 6.60 (s, 1H), 7.16 (dd, J=5.4, 8.4 Hz, 1H), 7.64 (dd, J=1.0, 6.5 Hz, 1H), 8.48 (dd, J=1.0, 5.4 Hz, 1H); MS (CI/NH_3) m/z: 215 $(M + H)^+$.

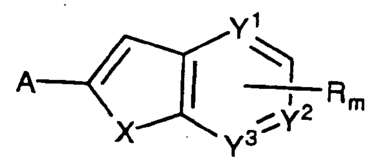
52g (±)-2-(7-aza-2-*exo*-bicyclo[2.2.1]heptyl)furo[3,2-b]pyridine dihydrochloride



The compound from step 52f above (219 mg, 1.02 mmol) was dissolved in Et_2O and a saturated solution of HCl in Et_2O was added dropwise. The solvent was removed and the precipitate was triturated with Et_2O (3X) then placed under vacuum to afford the title compound as white solid (245 mg, 80%): ^1H NMR (D_2O, 300 MHz) δ 1.85-2.32 (m, 7H), 3.77 (dd, J=5.8, 9.5 Hz, 1H), 4.47 (m, 1H), 4.65 (d, J=3.8 Hz, 1H), 7.07 (s, 1H), 7.64 (dd, J=5.4, 8.5 Hz, 1H), 8.30 (dd, J=1.0, 6.5 Hz, 1H), 8.55 (dd, J=1.0, 5.8 Hz, 1H); MS (CI/NH_3) m/z: 215 $(M+H)^+$, 232 $(M+NH_4)^+$; Anal. Calcd for $C_{13}H_{14}N_2O{\cdot}2.0HCl{\cdot}0.8H_2O$: C, 51.77; H, 5.88; N, 9.29. Found: C, 51.81; H, 5.66; N, 9.07.

WE CLAIM:

1. A compound of formula (I):

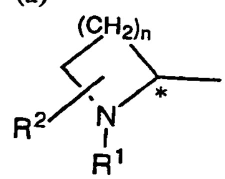


(I)

or a pharmaceutically acceptable salt or pro-drug thereof wherein:

A is selected from the group consisting of:

(a)



wherein

* denotes a chiral center,

m is 0, 1 or 2;

n is 1, 2 or 3,

R^1 is selected from the group consisting of H and C_1-C_3-alkyl, and

R^2 is H, or when n is 2 or 3 is selected from the group consisting of

C_1-C_3-alkyl,

C_1-C_3-alkoxyl,

hydroxymethyl,

fluoromethyl,

methoxymethyl,

Br,

Cl,

F,

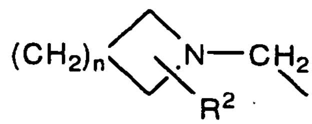
OH,

CN,

-O-CO-CH_3 and

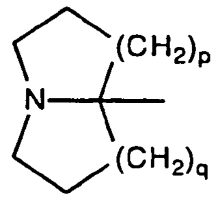
-O-methanesulfonyl;

(b)



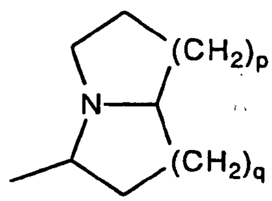
;

(c)



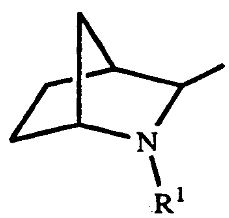
wherein p and q are independently 1 or 2;

(d)



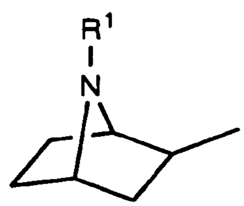
wherein p and q are independently 1 or 2;

(e)



, and

(f)



;

R is independently selected at each occurrence from the group consisting of

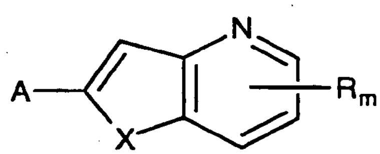
C_1-C_4-alkyl,
bromo,
chloro,
fluoro,
trifluoro-C_1-C_4-alkyl,
trichloro-C_1-C_4-alkyl,
COOH,
CO_2-C_1-C_4-alkyl,

CN,
nitro,
amino,
NH-CO-C_1-C_3-alkyl, and
NR^3R^3, wherein R^3 is H or C_1-C_3-alkyl;

X is -O-, -S- or -NR^3, wherein R^3 is H or C_1-C_3-alkyl;

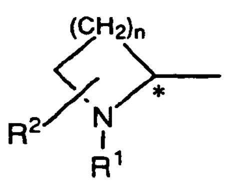
Y^1, Y^2 and Y^3 are N or CH, with the provisos that at least one of Y^1, Y^2 and Y^3 must be N and when group A is selected from option (b), then Y^2 and Y^3 must be CH.

2. A compound as defined by Claim 1 having the formula



or a pharmaceutically acceptable salt or pro-drug thereof.

3. A compound as defined by Claim 2 wherein A is selected from the group consisting of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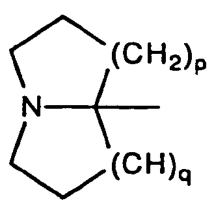
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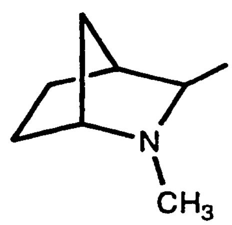
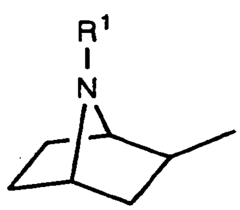

and

,

or a pharmaceutically acceptable salt or pro-drug thereof.

4. A compound defined by Claim 3 wherein R is selected from the group consisting of H, Cl and C_1-C_4-alkyl or a pharmaceutically acceptable salt or pro-drug thereof.

5. A compound as defined by Claim 1 selected from the group consisting of
2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
2-(2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;

2-(1-methyl-2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)-5-methylfuro[3,2-b]pyridine;
2-(1-methyl-2-(S)-pyrrolidinyl)-5-methylfuro[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)-6-chlorofuro[3,2-b]pyridine;
2-(1-methyl-2-(S)-pyrrolidinyl)-6-chlorofuro[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)furo[2,3-c]pyridine;
2-(1-methyl-2-(S)-pyrrolidinyl)furo[2,3-c]pyridine;
2-(2-(S)-pyrrolidinyl)-5-chlorofuro[3,2-b]pyridine;
2-(1-methyl-2-(S)-pyrrolidinyl)-5-chlorofuro[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)-5-chlorofuro[2,3-b]pyridine;
2-(1-methyl-2-(S)-pyrrolidinyl)-5-chlorofuro[2,3-b]pyridine;
2-(hexahydro-1H-7a-pyrrolizinyl)furo[3,2-b]pyridine;
2-(hexahydro-1H-7a-pyrrolizinyl)-5-methylfuro[3,2-b]pyridine;
2-(hexahydro-1H-7a-pyrrolizinyl)furo[2,3-c]pyridine;
endo-2-(hexahydro-1H-3-(R)-pyrrolizidinyl)furo[2,3-c]pyridine;
exo-2-(hexahydro-1H-3-(S)-pyrrolizidinyl)furo[2,3-c]pyridine;
exo-2-(hexahydro-1H-3-(R)-pyrrolizidinyl)furo[2,3-c]pyridine;
endo-2-(hexahydro-1H-3-(S)-pyrrolizidinyl)furo[2,3-c]pyridine;
1-pyrrolidinylmethyl-(2-furo[3,2-b]pyridine);
5-chloro-2-(hexahydro-1H-7a-pyrrolizinyl)furo[3,2-b]pyridine;
2-(hexahydro-1H-7a-pyrrolizinyl)thieno[3,2-b]pyridine;
5,6-dichloro-2-(2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
5,6-dichloro-2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
2-(hexahydro-1H-7a-pyrrolizinyl)-4-methylthieno[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)-5-bromofuro[3,2-b]pyridine;
2-(2-(R)-pyrrolidinyl)-5-methylfuro[3,2-b]pyridine;
2-(1-methyl-2-(R)-pyrrolidinyl)-5-methylfuro[3,2-b]pyridine;
2-(2-(R)-pyrrolidinyl)-6-chlorofuro[3,2-b]pyridine;
2-(1-methyl-2-(R)-pyrrolidinyl)-5-chlorofuro[3,2-b]pyridine;
2-(2-(R)-pyrrolidinyl)-5-bromofuro[3,2-b]pyridine;
2-(2-(R)-pyrrolidinyl)furo[2,3-c]pyridine;
2-(2-(S)-pyrrolidinyl)-furo[3,2-b]pyridine-5-carboxylic acid;
2-(1-methyl-2-(S)-pyrrolidinyl)-6-trifluoromethylfuro[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)-5-aminofuro[3,2-b]pyridine;
2-(1-methyl-2-(S)-pyrrolidinyl)-5-(acetylamino)furo[3,2-b]pyridine;
2-(1-methyl-2-(S)-pyrrolidinyl)-5-(diethylamino)furo[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)-5-trichloromethylfuro[2,3-b]pyridine;
2-(2-(S)-pyrrolidinyl)-5-(methoxycarbonyl)furo[2,3-c]pyridine;
2-(1-methyl-2-(S)-pyrrolidinyl)-4-cyanofuro[2,3-c]pyridine;

2-(1-methyl-2-(S)-pyrrolidinyl)-4-nitrofuro[2,3-c]pyridine;
2-(2-(R)-pyrrolidinyl)-5-chlorofuro[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)furo[2,3-b]pyridine;
2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-c]pyridine;
2-(hexahydro-1H-7a-pyrrolizinyl)-5,6-dichlorofuro[3,2-b]pyridine;
5,6-dichloro-2-(2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
5,6-dichloro-2-(1-methyl-2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
2-((1R,4S)-2-aza-3-(S)-bicyclo[2.2.1]heptyl)-2-furo[3,2-b]pyridine;
2-((1R,4S)-2-aza-3-(S)-bicyclo[2.2.1]heptyl)-2-methyl-2-furo[3,2-b]pyridine;
2-((1R,4S)-2-aza-3-(S)-bicyclo[2.2.1]heptyl)-5-chloro-2-furo[3,2-b]pyridine;
2-((1R,4S)-2-aza-3-(S)-bicyclo[2.2.1]heptyl)-5-chloro-2-methyl-2-furo[3,2-b]pyridine;
2-((1R,4S)-2-aza-3-(S)-bicyclo[2.2.1]heptyl)-5,6-dichloro-2-furo[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)-6-bromofuro[3,2-b]pyridine;
6-bromo-2-(2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
6-bromo-2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
6-bromo-5-chloro-2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
6-bromo-5-chloro-2-(2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
6-bromo-5-chloro-2-(1-methyl-2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
7-chloro-2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine; and
(±)-2-(7-aza-2-exo-bicyclo[2.2.1]heptyl)furo[3,2-b]pyridine; or

a pharmaceutically acceptable salt or prodrug thereof.

6. A compound as defined by Claim 3 selected from the group consisting of

2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
2-(2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
2-(1-methyl-2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)-5-methylfuro[3,2-b]pyridine;
2-(1-methyl-2-(S)-pyrrolidinyl)-5-methylfuro[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)-6-chlorofuro[3,2-b]pyridine;
2-(1-methyl-2-(S)-pyrrolidinyl)-6-chlorofuro[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)-5-chlorofuro[3,2-b]pyridine;
2-(1-methyl-2-(S)-pyrrolidinyl)-5-chlorofuro[3,2-b]pyridine;
5-chloro-2-(hexahydro-1H-7a-pyrrolizinyl)furo[3,2-b]pyridine;
2-(hexahydro-1H-7a-pyrrolizinyl)thieno[3,2-b]pyridine;

5,6-dichloro-2-(2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
5,6-dichloro-2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
2-(hexahydro-1H-7a-pyrrolizinyl)-4-methylthieno[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)-5-bromofuro[3,2-b]pyridine;
2-(2-(R)-pyrrolidinyl)-5-methylfuro[3,2-b]pyridine;
2-(1-methyl-2-(R)-pyrrolidinyl)-5-methylfuro[3,2-b]pyridine;
2-(2-(R)-pyrrolidinyl)-6-chlorofuro[3,2-b]pyridine;
2-(1-methyl-2-(R)-pyrrolidinyl)-5-chlorofuro[3,2-b]pyridine;
2-(2-(R)-pyrrolidinyl)-5-bromofuro[3,2-b]pyridine;
2-(2-(R)-pyrrolidinyl)-5-chlorofuro[3,2-b]pyridine;
2-(hexahydro-1H-7a-pyrrolizinyl)-5,6-dichlorofuro[3,2-b]pyridine;
5,6-dichloro-2-(2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
5,6-dichloro-2-(1-methyl-2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
6-bromo-2-(2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
6-bromo-2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
6-bromo-5-chloro-2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
6-bromo-5-chloro-2-(2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
6-bromo-5-chloro-2-(1-methyl-2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
7-chloro-2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
(±)-2-(7-aza-2-exo-bicyclo[2.2.1]heptyl)furo[3,2-b]pyridine; and
2-((1R,4S)-2-aza-3-(S)-bicyclo[2.2.1]heptyl)-2-methyl-2-furo[3,2-b]pyridine; or

a pharmaceutically acceptable salt or prodrug thereof.

7. A compound as defined by Claim 4 selected from the group consisting of

2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
2-(2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
2-(1-methyl-2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)-5-methylfuro[3,2-b]pyridine;
2-(1-methyl-2-(S)-pyrrolidinyl)-5-methylfuro[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)-6-chlorofuro[3,2-b]pyridine;
2-(1-methyl-2-(S)-pyrrolidinyl)-6-chlorofuro[3,2-b]pyridine;
2-(2-(S)-pyrrolidinyl)-5-chlorofuro[3,2-b]pyridine;
2-(1-methyl-2-(S)-pyrrolidinyl)-5-chlorofuro[3,2-b]pyridine;
5-chloro-2-(hexahydro-1H-7a-pyrrolizinyl)furo[3,2-b]pyridine;
5,6-dichloro-2-(2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
5,6-dichloro-2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;

2-(2-(R)-pyrrolidinyl)-5-methylfuro[3,2-b]pyridine;
2-(1-methyl-2-(R)-pyrrolidinyl)-5-methylfuro[3,2-b]pyridine;
2-(2-(R)-pyrrolidinyl)-6-chlorofuro[3,2-b]pyridine;
2-(1-methyl-2-(R)-pyrrolidinyl)-5-chlorofuro[3,2-b]pyridine;
2-(2-(R)-pyrrolidinyl)-5-chlorofuro[3,2-b]pyridine;
2-(hexahydro-1H-7a-pyrrolizinyl)-5,6-dichlorofuro[3,2-b]pyridine;
5,6-dichloro-2-(2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
5,6-dichloro-2-(1-methyl-2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
7-chloro-2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
6-bromo-2-(2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
6-bromo-2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
6-bromo-5-chloro-2-(1-methyl-2-(S)-pyrrolidinyl)furo[3,2-b]pyridine;
6-bromo-5-chloro-2-(2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
6-bromo-5-chloro-2-(1-methyl-2-(R)-pyrrolidinyl)furo[3,2-b]pyridine;
(±)-2-(7-aza-2-exo-bicyclo[2.2.1]heptyl)furo[3,2-b]pyridine; and
2-((1R,4S)-2-aza-3-(S)-bicyclo[2.2.1]heptyl)-2-methyl-2-furo[3,2-b]pyridine; or

a pharmaceutically acceptable salt or prodrug thereof.

8. A pharmaceutical composition comprising an amount if a compound as defined by Claim 1 effective to control chemical synaptic transmission in a mammal in combination with a pharmaceutically acceptable carrier.

9. A method of controlling chemical synaptic transmission in a mammal comprising administering to a mammal in need of such treatment an effective amount of a compound as defined by Claim 1.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/12274

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D491/044 C07D519/00 A61K31/435 C07D471/04
//(C07D491/044,307:00,221:00),(C07D519/00,491:00,487:00),
(C07D519/00,495:00,487:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JOURNAL OF MEDICINAL CHEMISTRY, vol. 38, no. 3, 1995, WASHINGTON US, pages 473-487, XP002017103 B.M. NILSSON ET AL.: "3-Heteroaryl-substituted quinuclidin-3-ol and quinuclidin-2-ene derivatives as muscarinic antagonists. Synthesis and structure-activity relationships" see table 3	1,8

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
29 October 1996	06.11.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Alfaro Faus, I

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 96/ 12274

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 9 is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.